Recyclable chiral auxiliaries for asymmetric synthesis

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Recyclable chiral auxiliaries for asymmetric synthesis

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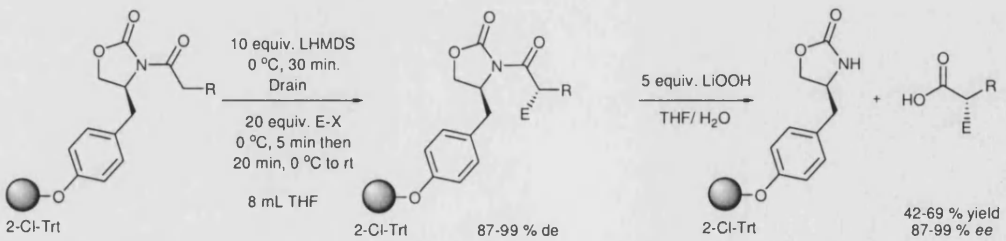
Abstract

Asymmetric synthesis on polymer support remains a relatively underdeveloped area of organic chemistry. Recently, interest has grown in the development of polymer-supported chiral auxiliaries and a review of the literature in this area demonstrates that efficient asymmetric synthesis using a polymer-supported chiral auxiliary is possible. However, in most cases, there are issues associated with the transfer of solution phase techniques to solid supported systems and reaction conditions need to be re-optimised.

This study aimed to develop an efficient and versatile polymer-supported chiral auxiliary based on the Evans oxazolidin-2-one. Phenolic oxazolidin-2-one fragment **1** was immobilised onto 2-chlorotrityl-chloride resin; the latter being selected as a development resin due to its orthogonal cleavage properties. Preliminary studies developed techniques to effect cleavage of the solid-supported species at various sites to enable solution phase characterisation of solid-phase intermediates, and thus facilitate optimisation of the solid-phase asymmetric reaction.

1 **2**

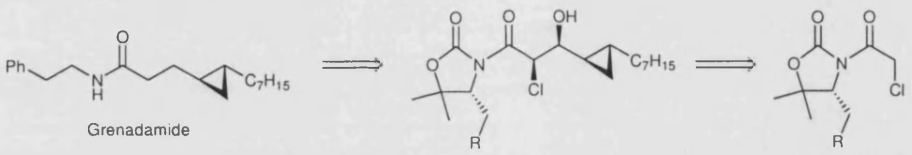
2-Cl-Trt supported oxazolidin-2-one **2** was firstly applied to an asymmetric enolate alkylation reaction. It was found that the reaction had conflicting temperature and time requirements for enolate reactivity versus enolate decomposition. In addition, it was discovered that the use of excess base could cause epimerisation of the newly formed stereocentre of the α-alkylated product, although this issue could be avoided by a slight alteration to the reaction conditions. The optimised conditions allowed an array of α-alkylated acids to be prepared in good yields and excellent enantioselectivity. In addition, it was shown that the resin could be recycled up to three times with no loss in stereoselectivity and only slight loss in yield.



Scheme i): *Optimised reaction conditions for the asymmetric enolate alkylation reaction of the enolates of polymer–supported N-acyl-oxazolidin-2-ones.*

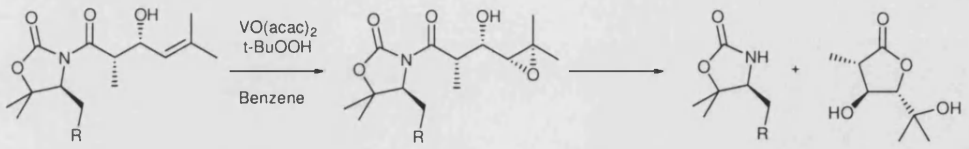
Attempts to develop a Merrifield resin supported version of this auxiliary were less successful, as the alteration to the solid support caused a marked decrease in the levels of diastereoselectivity achieved in the subsequent asymmetric reaction. Preliminary investigations into 2-Cl-Trt supported SuperQuat auxiliaries suggested they too could achieve high levels of diastereoselectivity in polymer-supported asymmetric enolate alkylation reactions and due to their superior cleavage profile compared to Evans-oxazolidin-2-ones, could in some cases offer advantages over the latter.

Finally, early investigations into new strategies for the use of Evans oxazolidin-2-one type auxiliaries, both in solid and solution phase were conducted. The stereodefined hydroxyl group of an Evans-oxazolidin-2-one aldol product was used to direct a second asymmetric reaction, thus the oxazolidin-2-one fragment indirectly induced chirality at a site remote to its normal area of influence. This strategy was demonstrated in the solution phase synthesis of a cyclopropane-containing natural product Grenadamide and the key directed cyclopropanation reaction was also demonstrated on a solid supported aldol product, prepared *via* a solid-phase aldol reaction.



Scheme ii): *Retrosynthesis of Grenadamide.*

A similar strategy employed a directed epoxidation reaction on polymer-supported allylic alcohols (again prepared *via* oxazolidin-2-one-mediated aldol reactions, which resulted in the formation of chiral γ-lactones in high de *via* an epoxidation / intramolecular cyclisation mechanism. Again, preliminary experiments into the analogous solid phase reaction gave promising results.



Scheme iii) *Synthesis of chiral γ-lactones* via *an epoxidation / intramolecular cyclisation mechanism.*

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Acknowledgements

Firstly I'd like to thank Steve Bull for his help, guidance, friendship and enthusiasm throughout and for making every unexpected result an opportunity!

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A special mention for Kate, a wonderful friend and housemate throughout and thank you to my family, who have smiled and nodded at all my chemistry rants, but have none the less been very supportive. Not sure how they are going to attach this thesis to the fridge door though.

Finally, a huge thank you to my Lovely fiancé (!) Richard, who has picked up the pieces so many times yet still manages to believe in me. We can have our weekends back now!

Abbreviations

app.	Apparent
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*Tert*-butoxy carbonyl
br.	Broad
Bu	Butyl
° C	Degrees celcius
^{13}C – NMR	Carbon nuclear magnetic resonance
cat.	Catalytic
CI	Chemical ionisation
d	Doublet
δ	NMR chemical shift
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet of doublets
de	Diastereomeric excess
dil.	Dilute
DIPEA	Diisopropylethylamine
DMAP	*N*-Dimethylaminopyridine
DMF	Dimethylformamide
ee	Enantiomeric excess
equiv.	Equivalents
ES	Electrospray
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier Transform Infra Red spectroscopy
g	Gram

hr	Hours
^{1}H-NMR	Hydrogen nuclear magnetic resonance
HPLC	High performance liquid chromatography
Hz	Hertz
in vacuo	Under vacuum
i-Pr	*Iso*-propyl
IR	Infrared
J	Coupling constant
LDA	Lithium diisopropylethylamine
LHMDS	Lithium hexamethyl disilazide
m	Multiplet
M^+	Molecular ion
Me	Methyl
MeOH	Methanol
Mes	Mesyl / Methane sulfonyl
mg	Milligram
min	Minutes
mL	Millilitre
mmol	Millimole
mp	Melting point
m/z	mass/charge ratio
NMR	Nuclear magnetic resonance
P	Protecting group
Ph	Phenyl
ppm	Parts per million
ps	Poly(styrene)
quart.	Quartet
rt	Room temperature
s	Singlet
t	Triplet
TBDMS	*Tert*-butyl dimethylsilyl

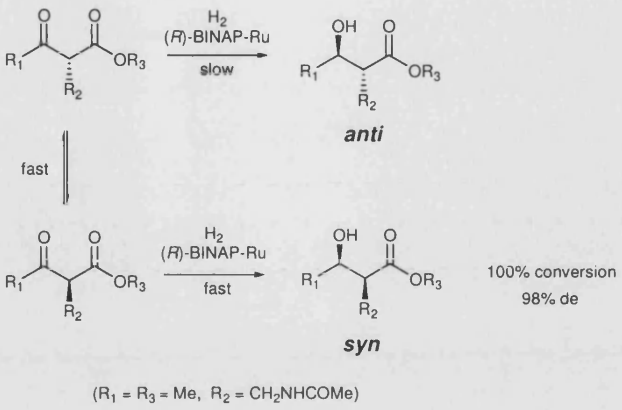
t-Bu	*Tert*-butyl
Tf	Trifluoromethyl sulfonyl
TFA	Trifluoroacetic acid
TFMSA	Trifluoromethane sulfonic acid
THF	Tetrahydrofuran
TIS	Triisopropylsilane
TLC	Thin layer chromatography
υ	Frequency

Chapter 1 Asymmetric polymer-supported organic synthesis.

1.1 Introduction

There are only three fundamentally different methods for preparing enantiomerically pure compounds: resolution, use of enantiopure starting materials available from the pool of chiral natural products and the use of asymmetric transformations.[1]

Resolution involves the separation of a racemic mixture of two enantiomers and can be achieved *via* a number of methods including formation of diastereomers, enzymatic resolution and kinetic resolution. Each of these techniques suffers an inherent drawback in that the maximum possible yield of any one enantiomer is just 50%, however the fact that often both enantiomers can be isolated can be a significant advantage. Dynamic kinetic resolution, which combines a kinetic resolution of two enantiomers with an *in situ* racemisation of the unwanted enantiomer, can (in principle) afford the desired enantiomer in 100% ee and 100% yield (for example, see scheme 1.1a).



Scheme 1.1a: *First published example of chemical dynamic kinetic resolution by Noyori* et al.[2] *Syn-aldols formed in excellent yield and de.*

The use of chiral pool starting materials such as amino acids, terpenes and steroids (see Fig. 1.1a.) can be a reliable method of introducing asymmetry into a system. However, obvious limitations include the existence and availability of the correct enantiomer of a suitable starting material whilst extensive modifications to remove or introduce functional groups can significantly lengthen synthetic protocols.

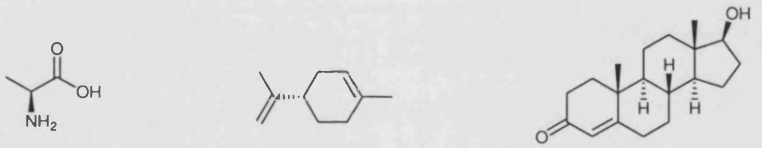
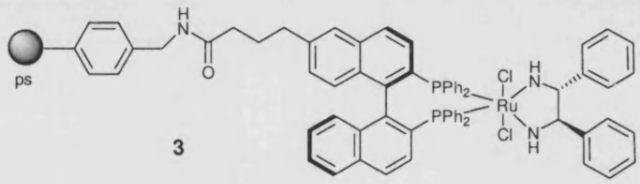


Fig 1.1a: *(S)-alanine, (S)-limonene and testosterone: an amino acid, a terpene and a steroid respectively.*

Asymmetric transformations involve the introduction of asymmetry into a prochiral system. This is achieved by incorporating a chiral component into a reagent/catalyst or into the substrate itself and then using this chirality to induce asymmetry in a subsequent chemical reaction. This results in diastereomeric transition states of differing energy, which can allow one enantiomer to be formed preferentially. This approach represents a more versatile option than the use of chiral pool starting materials and also has the potential to form a single enantiomer in 100% yield.

Asymmetric transformations can be divided into three categories, involving the use of chiral reagents, chiral catalysts or chiral auxiliaries. Chiral reagents and chiral catalysts

can transform prochiral substrates to produce single enantiomers of chiral products with excellent levels of enantioselectivity. It is often suggested that chiral catalysts hold an advantage over chiral reagents as the former can be used in sub-stoichiometric quantities as they are regenerated in the reaction cycle, affording them the potential to be recycled (as demonstrated by example in Scheme 1.1b). Chiral reagents on the other hand, require the use of stoichiometric quantities and are generally consumed in the reaction.



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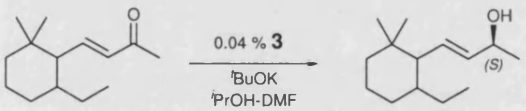


Catalyst reuse No	Time (h)	Conversion (%)	ee (%)
1	15	100	84
6	30	100	83
11	72	100	87

Scheme 1.1b: *Asymmetric reduction of conjugated ketone with polystyrene (ps)-supported BINAP catalyst* **3** *as reported by Noyori et al.*[2] *Catalyst* **3** *could be recycled at least 11 times with no loss in selectivity, however increasingly longer reaction times were required to achieve high conversions.*

The use of chiral auxiliaries represents a different strategy, with the source of chirality being reversibly incorporated into the substrate itself. A chiral auxiliary (CA) is an enantiomerically pure compound that is temporarily attached to a prochiral substrate (S) in order to exert stereocontrol in a subsequent reaction with achiral reagents. Following the asymmetric reaction, the chiral auxiliary is removed from the product (CA-P), leaving an enantiomeric product (P) and recovering the chiral auxiliary (CA), see Fig. 1.1b. Again, excellent levels of stereoselectivity can be achieved.

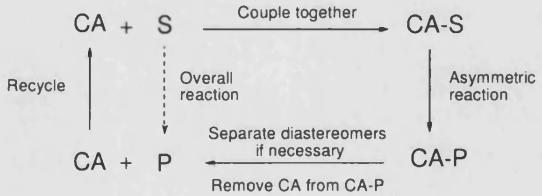


Fig 1.1b: *General chiral auxiliary strategy where* CA = *chiral auxiliary,* S = *substrate,* P = *product.*

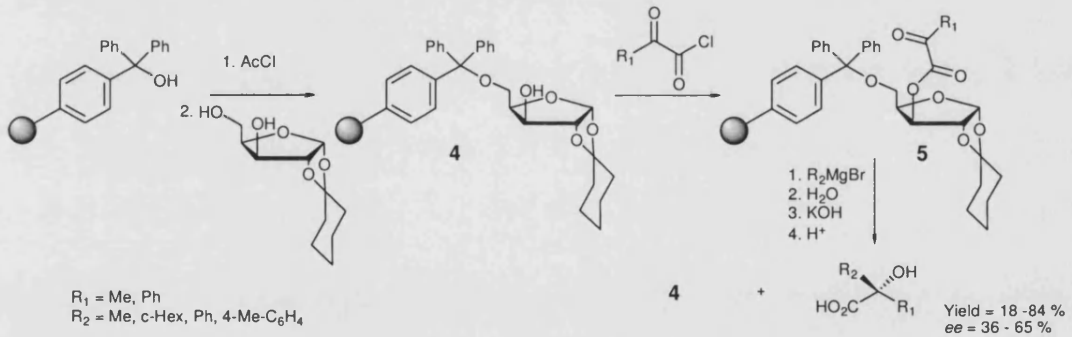
In such asymmetric reactions, the ability to recycle stoichiometric amounts of the chiral auxiliary fragment is crucial to the cost-effectiveness of the system; however in practice, its efficient recovery and reuse is often difficult to achieve. It is perhaps for this reason that a renewed interest in developing solid-phase asymmetric reactions has emerged over the last 15 years. As well as the significant benefit of facile recovery and recycling of the auxiliary, other advantages of solid phase reactions apply. These include purification being achieved by simple filtrations and the use of excess reagents to be drive reactions to completion. It has also been proposed that the microenvironment of the polymeric support may potentially lead to increased levels of stereoselectivity in the asymmetric reaction.[3,4]

Consequently, extensive work has been undertaken towards the development of solid-supported chiral auxiliaries and many successful systems have been identified. Comprehensive reviews exist covering all aspects of solid-supported asymmetric synthesis, including the use of polymer-bound chiral ligands with metal centres,[5] polymer-supported chiral organic catalysts [6] and polymer-supported chiral auxiliaries.[7] As in solution phase, a successful polymer-supported chiral auxiliary suffers some disadvantages when compared to a successful polymer-supported catalytic system. For example, stoichiometric quantities of chiral auxiliaries are required whereas catalysts are generally employed in sub-stoichiometric amounts. Additionally, the use of a chiral auxiliary necessarily adds another two steps to the reaction sequence during addition and removal of the auxiliary fragment. However, catalysts, both in solution and solid-phase have often been found to be highly substrate and reaction specific resulting in reaction failure or loss of stereocontrol. Chiral auxiliaries on the other hand, often demonstrate a greater degree of versatility, with high tolerances for different substrates and the ability to be applied to several different types of asymmetric reaction. For this reason, it was decided to focus the following literature review, and the subsequent research work on polymer-supported chiral auxiliaries. It should be noted that this literature review is by no means exhaustive but aims to highlight some of the more interesting results achieved in recent years, focussing on the accessibility of the methodology to a non-specialist organic chemist and the effect of the solid support upon the reaction. In the vast majority of cases, the chiral auxiliary (or an immediate precursor) is prepared in solution phase and attached to the polymer support as a final synthetic step. In

the interests of brevity, full details of the synthesis of the chiral auxiliaries before their attachment to polymer support are not included in this review.

1.2 Early examples of polymer-supported chiral auxiliaries

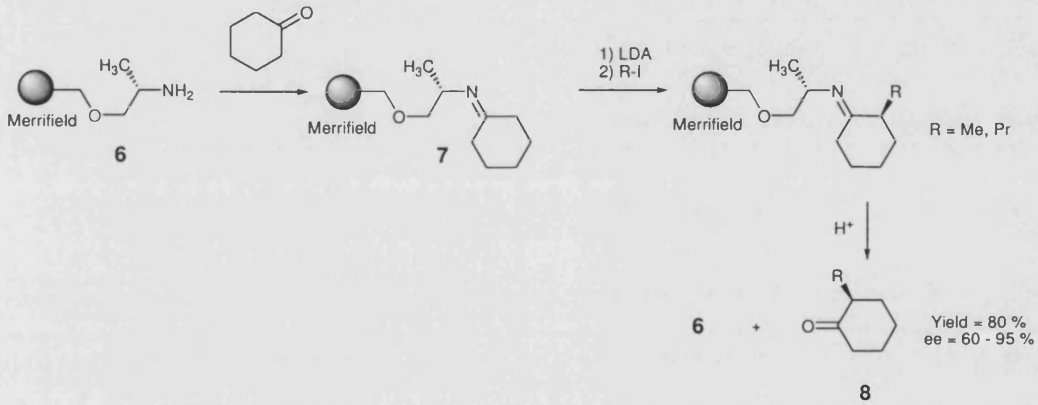
In 1972, Kawana *et al.* reported the first example of a polymer-supported chiral auxiliary in asymmetric synthesis, [8] with additional examples provided in a subsequent report in 1974.[3] In this work, both D- and L-1,2-*O*-cyclohexylidene-α-xylofuranose were used as chiral auxiliaries in the asymmetric synthesis of α-hydroxy acids (see Scheme 1.2a, D-form shown). The auxiliary fragments, prepared in 2 steps from D- and L-xylose respectively, were immobilised onto trityl resin in 73 - 87% yield *via* their primary hydroxyl group. Esterification of immobilised auxiliary **4** with either benzoylformic acid or pyruvic acid afforded α-ketoesters **5** which were then treated with a Grignard reagent. After hydrolysis of the resulting product, a range of α-hydroxy acids were obtained in yields of 18–84% and *ee*'s of 36-65%. The authors reported that in many cases, these results were superior to those gained in the analogous solution phase reaction. Importantly, it was also reported that resin **4** could be recycled at least seven times with no decrease in the yield or enantioselectivity.



Scheme 1.2a: *The first example of a polymer-supported chiral auxiliary to produce chiral α-hydroxy acids as reported by Kawana et al.*

A second, successful system was reported by Leznoff *et al.* in 1979, this time employing a polymer-supported alaninol derived auxiliary in the asymmetric α-alkyation of imines of cyclohexanone.[9] The polymer-bound auxiliary **6** was readily prepared in just three steps by attachment of *N*-phthalimide protected L-alaninol to Merrifield resin under basic conditions

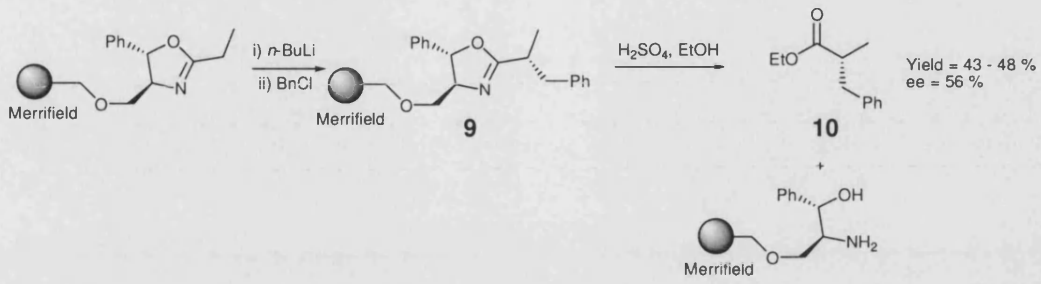
and subsequent *N*-deprotection. In this case, the resulting resin was treated with tri-*n*-butyl-tin hydride to remove any un-reacted chlorobenzyl groups present that might interfere with the subsequent alkylation reaction. Attachment of the cyclohexanone substrate as its imine **7** was followed by deprotonation with LDA (at 0 °C), quenching of the enolate at room temperature with an electrophile and finally acidic hydrolysis, to afford α-alkyated cyclohexanone **8** in 80% yield and 60 – 95% ee (see Scheme 1.2b). Again, it was found that the resin-bound auxiliary could be reused in subsequent reaction cycles with little loss of stereoselectivity, although the yields of α-alkylated cyclohexanone produced did decrease.



Scheme 1.2b: *Polymer-supported (L)-alaninol auxiliary* **6** *for the preparation of chiral α-alkyated cyclohexanones* **8**.

However, a third early report describing the immobilisation of the established solution phase oxazoline chiral auxiliary onto polymer-support proved to be less successful. McManus *et al.* attached a chiral oxazoline to Merrifield resin and alkylated its enolate at its α-position using benzyl chloride (see Scheme 1.2c).[10] However, attempts to hydrolyse product **9** to form α-benzylated ethyl ester **10** employing the standard solution phase method (H_2SO_4 in EtOH / THF) were unsatisfactory affording only low yields of **10**. Unfortunately, the use of harsher acidic cleavage conditions also resulted in cleavage of the auxiliary fragment from the polymer support. With incomplete cleavage occurring, not only were yields of product low in that cycle, but the recycling of the resin was effectively prevented. Therefore, although the oxazoline ring could be re-formed on polymer support, the presence of some un-hydrolysed products from the previous cycles lead to reduced

yields and contamination of the product. Additionally, the optical purity of the product (*ee* = 56%) was much lower than that reported for the analogous solution phase reaction.



Scheme 1.2c: *Application of a polymer-supported oxazoline auxiliary by McManus et al.*

These early results clearly showed that asymmetric synthesis on solid support and recycling of the polymer-bound auxiliary was possible. However, the problems encountered by McManus demonstrate that solution phase reaction conditions are not necessarily applicable to solid phase systems.

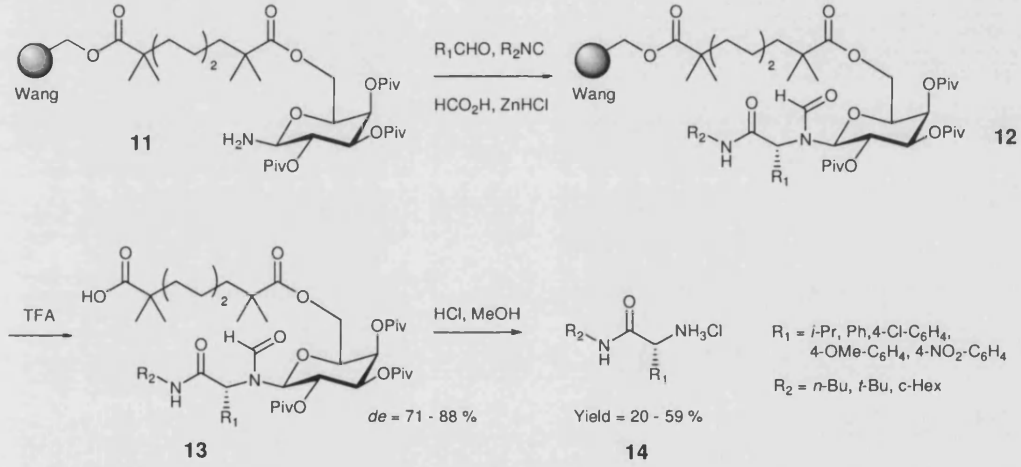
1.3 Recent examples of polymer-supported chiral auxiliaries

After these early accounts, there was a lull in further investigations into this field, until the early 1990s when several different types of immobilised auxiliaries were developed and applied to a variety of different reactions. A selection of these applications are described below, organised according to the nature of the polymer-bound auxiliary used for asymmetric synthesis.

1.3.1 Alcohol and carbohydrate-based auxiliaries

Kunz *et al.* reported an asymmetric Ugi four-component condensation involving chiral *O*-pivaloylated-galactosylamine **11** as a chiral auxiliary and 'asymmetric ammonia' equivalent (see Scheme 1.3.1a).[11] In order to synthesise the functionalised resin, *O*-pivaloylated-galactosylazide was attached to Wang resin *via* a tetramethylazelaic acid spacer and then reduced to its amine. It was found that shorter linkers resulted in sluggish Ugi reactions. A series of stereoselective Ugi four-component condensations, performed with five equivalents of aldehyde, isonitrile and formic acid under Lewis acid conditions led to the

formation of polymer-bound glycine amides **12**. However, due to the acid lability of the Wang resin support, it was not possible to cleave the enantiomeric products from the resin directly. Instead the entire auxiliary fragment was removed *via* treatment with TFA and the yields (20–59%) and *de*s (71–88%) of the diastereomeric products **13** determined. After purification, **13** was treated with hydrochloric acid in methanol to afford enantiomerically pure α-amino amides **14**. Subsequent application of the Ugi reaction conditions to a hydroxymethyl polystyrene-supported auxiliary resulted in a more stable ester linkage and allowed the direct cleavage of amides from solid support in similar stereoselectivities but reduced yields (30-33%).

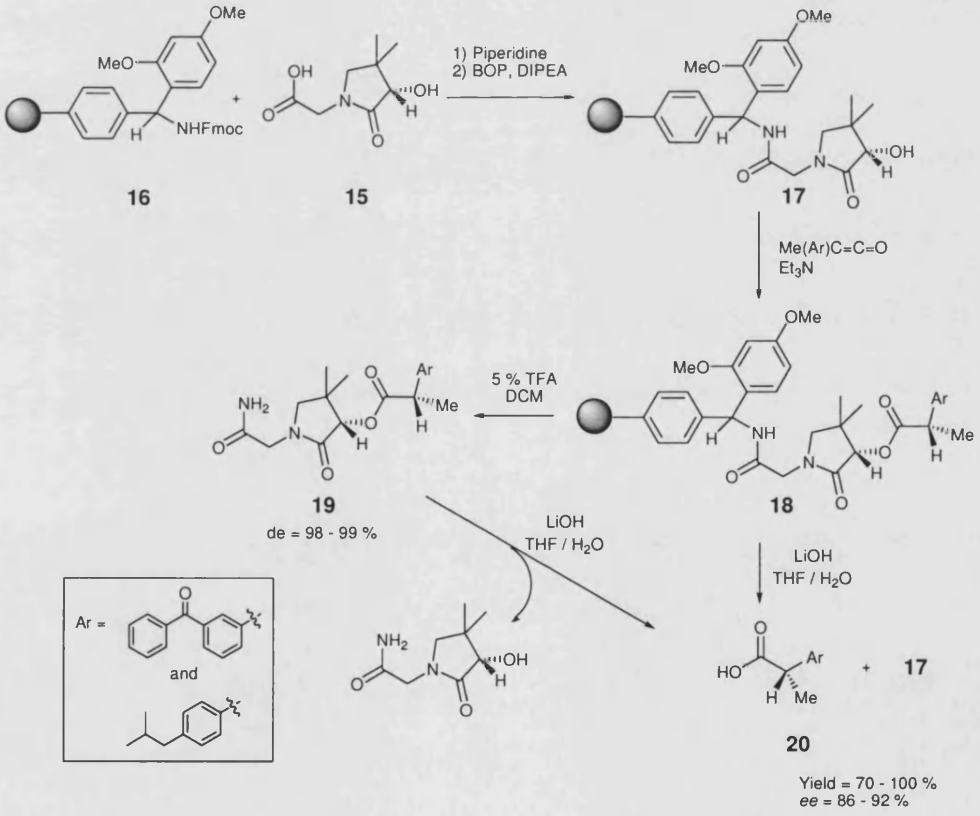


Scheme 1.3.1a: *Asymmetric Ugi four component condensation employing a polymer-supported chiral O-pivaloylated-galactosylamine-derived chiral auxiliary, as reported by Kunz and co-workers.*

Calmes and co-workers have reported the use of a polymer-supported pantolactone-based auxiliary for stereoselective reactions with prochiral ketenes [12,13] and later in Diels Alder cycloadditions.[14]

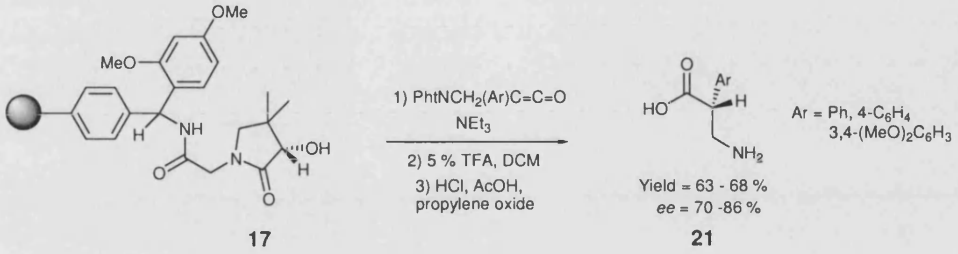
Synthesis of the auxiliary fragment **15** from pantolactone was lengthy, involving eight synthetic steps. The synthesis was initially achiral with the two enantiomers being separated *via* conversion to their (*S*)-camphoric esters, column chromatography of the resulting diastereomers and separate saponification of each compound. The overall yield of **15** was not given. After immobilisation of the carboxylate group of **15** onto Rink Amide resin **16**, the resultant polymer-supported auxiliary **17** was treated with ketene (pre-formed by treatment of the corresponding acid chloride with triethylamine) under basic conditions

to form polymer-supported chiral ester **18** (see Scheme 1.3.1b).[12] The judicious use of Rink amide resin enabled ester **18** to undergo orthogonal cleavage at two different sites. Acidic cleavage of the benzhydrylamine bond cleaved the entire auxiliary-substrate fragment **19** and allowed determination of the *de* of the chiral product. The option to cleave the product as the diastereomer also enabled purification or enrichment of the chiral product if moderate levels of stereocontrol were observed. Alternatively, basic hydrolysis afforded the desired chiral propionic fragment **20**. Although excellent diastereoselectivity in the asymmetric protonation reaction was observed (98 – 99% *de*), it was found that the basic hydrolysis step caused racemisation of the newly formed stereogenic centre and hence reduced the ee of the resulting chiral propionic acids **20**, in some cases affording racemic mixtures. Recycling of polymer-supported auxiliary **17**, easily recovered after saponification of **18**, and its use in a second asymmetric reaction afforded **20** in acceptable yield (70%) but good ee (84%), representing a slight decrease compared to the first cycle.



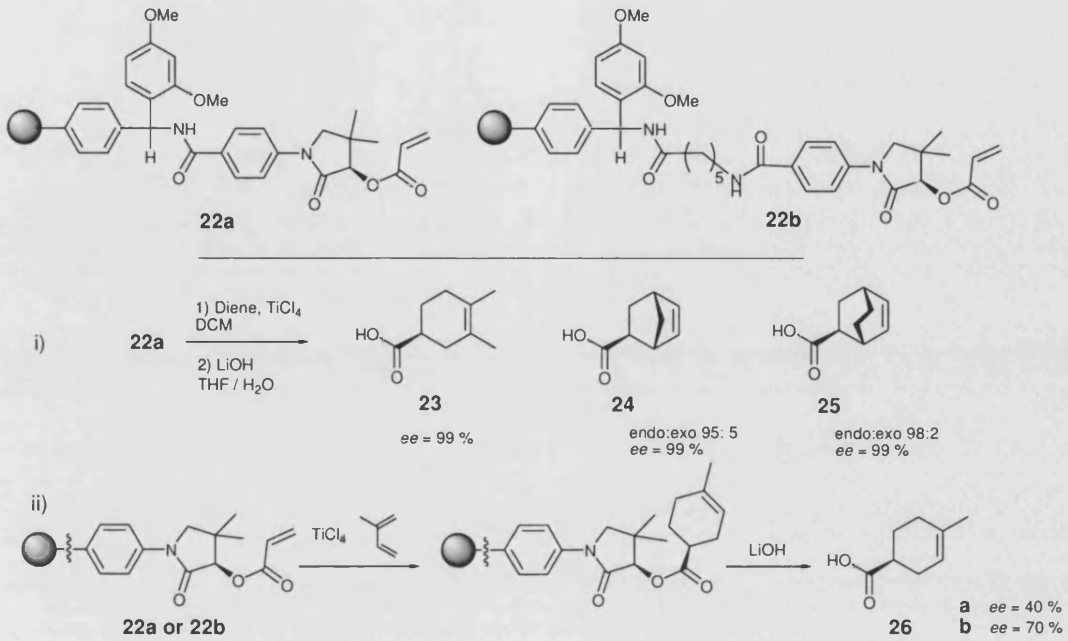
Scheme 1.3.1b: *Application of a solid-supported pantolactone-derived chiral auxiliary* **17** *in an asymmetric reaction with a prochiral ketene, as reported by Calmes et al.*

Polymer-supported chiral auxiliary **17** was also applied to the asymmetric synthesis of β^2-homoarylglycines **21**, according to a very similar method, see Scheme 1.3.1c.[13]



Scheme 1.3.1c: *Asymmetric synthesis of β^2-homoarylglycines* **21**, *as reported by Calmes et al.*

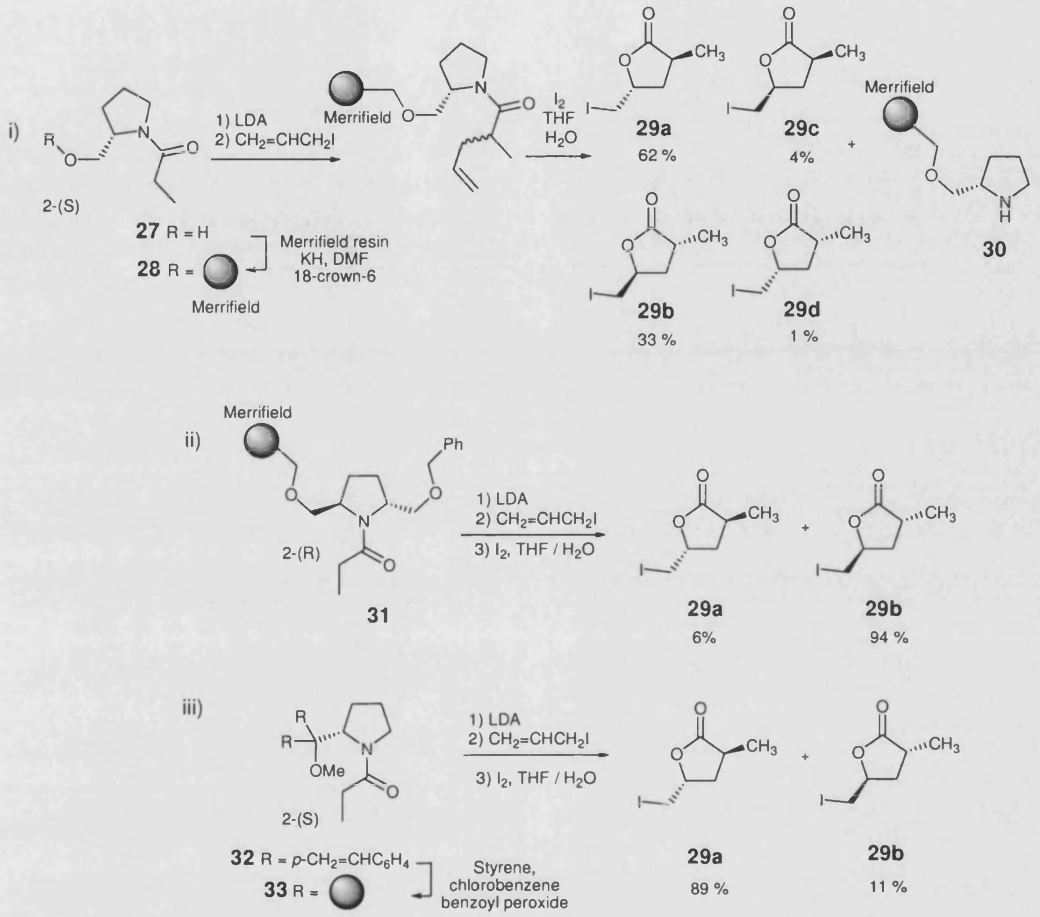
Calmes *et al.* have also reported the application of a structurally related auxiliary to asymmetric Diels Alder reactions (see Scheme 1.3.1d).[14] The second generation auxiliary incorporated an additional phenyl spacer unit with acrylate derivative **22a** being found to react with 2,3-dimethylbutadiene, cyclopentadiene and 1,3-cyclohexadiene in good yield and selectivity to afford **23**, **24** and **25** respectively after basic hydrolysis. In the Diels Alder reaction of **22a** with the less reactive diene isoprene, cycloadduct **26** was formed in a poor 40% *ee*. However, for the same reaction, the use of an alternative auxiliary **22b** which included an additional alkyl chain spacer resulted in an increase in the ee of acid **26** to 70%, suggesting that an increased distance between the chiral auxiliary and the polymer support was beneficial.



Scheme 1.3.1d: *The use of a polymer-supported pantolactone-derived auxiliary in asymmetric Diels Alder reactions, as described by Calmes et al.*

1.3.2 Amine and hydrazine derived auxiliaries

Schore and co-workers reported the use of a proline-derived solid-supported chiral auxiliary and its application in the synthesis of chiral 3,5-disubstituted-γ-butyrolactones in a three step process involving *N*-acylation, *C*-α-alkylation and iodocyclisation (see Scheme 1.3.2a, i).[15] Pentamide **27** (prepared in one step from L-prolinol and propionyl chloride) was immobilised onto Merrifield resin and the resulting resin **28** treated with LDA and allyl iodide to effect α-allylation of the resin-bound amide. The product of this reaction could not be monitored directly, but treatment with iodine afforded a mixture of the four possible α-substituted-γ-butyrolactones **29** in 33% yield, with the predominant product **29a** achieved in 32% ee. This result was reported to be similar to that obtained in solution phase using a proline chiral auxiliary of this type. Importantly, the cyclisation process simultaneously regenerated the reactive polymer supported auxiliary **30**, ready for subsequent *N*-acylation and use in further reactions. The authors showed that a second reaction cycle could be performed on the same batch of resin without any decrease in stereoselectivity although the yield of α-substituted-γ-butyrolactones prepared in the second cycle was not disclosed.



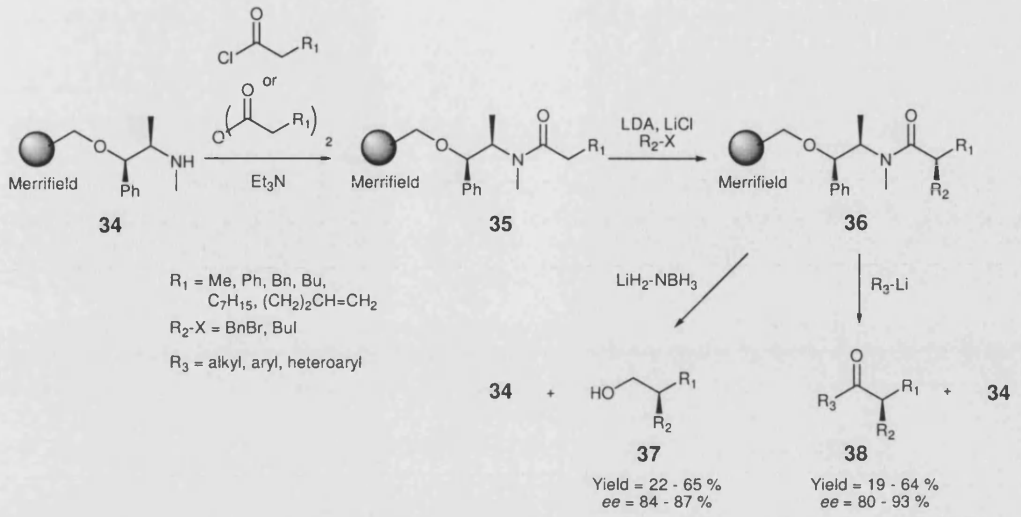
Scheme 1.3.2a: *Application of three generations of polymer supported proline-derived chiral auxiliaries for the synthesis of chiral 3,5-disubstituted-γ-butyrolactones, as described by Schore and coworkers.*

In a later report, the authors described an improved pseudo-C_2-symmetric polymer-supported chiral auxiliary, also derived from (L)-proline (see Scheme 1.3.2a *ii*).[16] In a similar reaction to that investigated previously, *N*-propionyl auxiliary **31** was α-alkylated and then treated with iodine to effect iodocyclisation with simultaneous cleavage of *trans*-2,5-disubstituted-γ-butyrolactone **29b** in 34% crude yield and 88% *ee*. In this case there was no sign of any of the *cis*-products, implying a highly selective iodocyclisation process.

In a third iteration, Schore and co-workers reported another variation of a (L)-proline derived polymer-supported chiral auxiliary, (see Scheme 1.3.2a, *iii*).[4] In this case, the

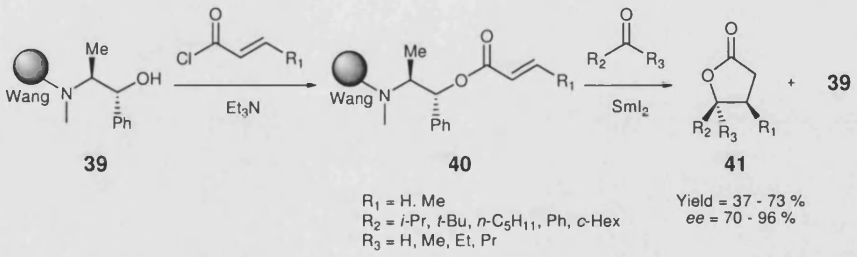
authors actually incorporated the chiral auxiliary as a cross-linker into the polystyrene support itself by using auxiliary **32** as a monomer in a suspension polymerisation reaction with styrene. The resulting α-substituted-γ-butyrolactone **29a** was prepared in 45% crude yield and 78% *ee*. This result is a significant improvement when compared to the results obtained for auxiliary **28** that had been prepared in a conventional manner. The authors proposed that chiral auxiliary **33**, cross-linked into the polymer matrix, was likely to experience a more constrained environment than a pendant-bound auxiliary fragment which, in this case, fortuitously resulted in enhanced stereocontrol. However, the authors note that there are also examples in the literature where the close proximity of the auxiliary to the polystyrene back bone has caused a reduction in stereoselectivity and hence conclusions regarding the merit of pendant- *versus* cross-linked chiral auxiliaries could not be drawn without further study.

Procter *et al.* have used polymer-supported pseudoephedrine as a chiral auxiliary in solid-phase asymmetric enolate alkylations (see Scheme 1.3.2b).[17,18] Pseudoephedrine was immobilised onto Merrifield resin selectively *via* its hydroxyl group, thus creating the polymer-supported chiral auxiliary **34** in just one step. The secondary amine group was then *N*-acylated with a variety of acid chlorides and anhydrides to give a small library of the corresponding polymer-supported amides **35**, which were subsequently deprotonated and alkylated using modified Myers' LDA-LiCl conditions to give α-alkylated amides **36** (see Scheme 1.3.2b). Further diversity was introduced by the use of different cleavage methods to release the chiral product from the resin. Primary alcohols **37** were obtained in moderate yield and good ee by cleavage of α-alkylated amides **36** with lithium amidotrihydroborate whilst chiral ketones **38** were obtained in moderate yield and good ee *via* treatment with alkyl-, aryl- or heteroaryl-lithium reagents. Importantly, the authors demonstrated that the pseudoephedrine resin **34** could be recycled at least three times with no significant loss in activity.



Scheme 1.3.2b: *Polymer-supported pseudoephedrine as a chiral auxiliary for solid-phase asymmetric enolate alkylations, as reported by Procter et al.*

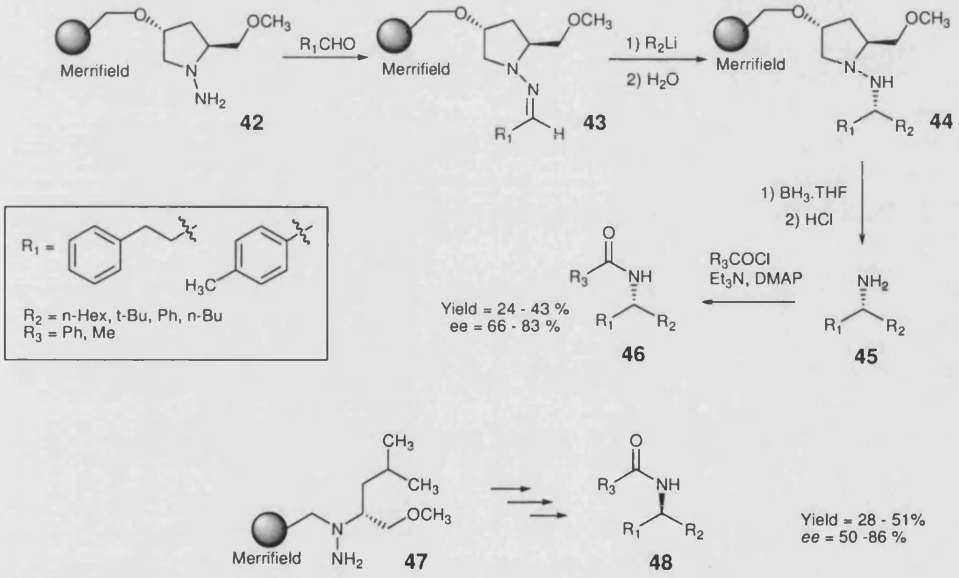
Procter and co-workers also reported the asymmetric synthesis of γ-butyrolactones **41** using polymer-supported ephedrine as a chiral linker (see Scheme 1.3.2c).[19] In this case, ephedrine was attached to Wang resin selectively *via* its amino functionality to form **39**, leaving the alcohol group free for subsequent esterification reactions to allow attachment of the chiral linker to the substrate. In this way, both acryloyl- and crotonoyl-esters **40** were prepared. Treatment of resin **40** with an aldehyde and SmI_2 at low temperatures resulted in a samarium (II)-mediated intermolecular ketyl-alkene addition between the aldehyde and the resin-bound α,β-unsaturated ester, with spontaneous cyclative cleavage from the resin to afford γ-butyrolactones **41** in moderate yield and high *ee*.



***Scheme 1.3.2c**: Application of polymer-supported ephedrine as a chiral linker in the asymmetric synthesis of γ-butyrolactones, as described by Procter et al.*

Enders *et al.* reported the use of two chiral hydrazine resins for the asymmetric synthesis of non-racemic α-branched primary amines (see Scheme 1.3.2d).[20] Two enantiopure β-

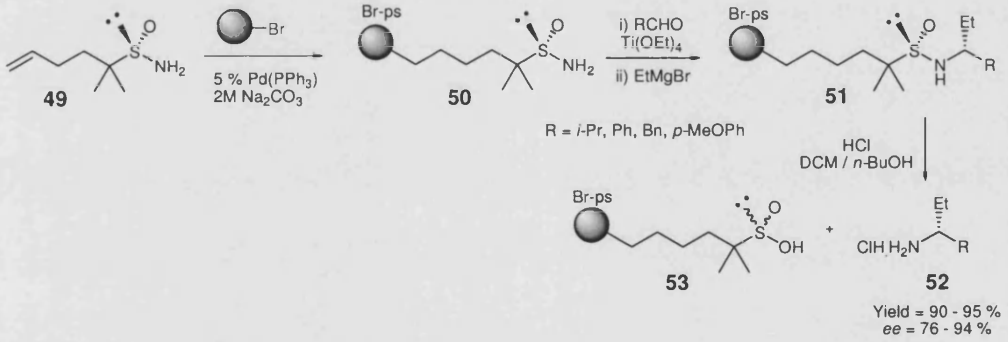
methoxyamino auxiliaries, derived from *trans*-hydroxy-(*S*)-proline and (*R*)-leucine respectively, were attached to Merrifield resin as their protected amines, then converted to the corresponding hydrazines *via* nitrosation and reduction with DIBAL-H. In the case of (*S*)-proline-derived auxiliary **42**, immobilisation of various aliphatic and aromatic aldehydes gave hydrazones **43**, with subsequent 1,2-addition of aliphatic and aromatic organolithium reagents to the C=N double bond to afford chiral hydrazines **44**. The chiral α-branched primary amines **45** were released from the resin *via* reductive borane cleavage. In order to determine the ee of the resulting chiral amines **45**, it was necessary to convert them to their benzoyl- or acetyl-amides for analysis *via* chiral HPLC, and it was found that amides **46** had been formed in moderate yields (24 - 43%) and acceptable *ee*s (66 – 83%). An identical procedure employing (*R*)-leucine-derived auxiliary **47** afforded chiral amides **48** of the opposite configuration, in similar yields (28 – 51%) and *ee*s (50 - 86%).



Scheme 1.3.2d: *The application of two chiral hydrazine resins* **42** *and* **47** *for the synthesis of chiral α-branched primary amines* **45** *as reported by Enders and co-workers.*

1.3.3 Sulfoxide and sulfinamide auxiliaries

Sulfur-containing compounds such as sulfoxides, sulfinamides and sulfinate esters have the potential to be chiral due to the presence of a stereogenic sulfur atom. Ellman and co-workers have developed a polymer-supported enantiopure sulfinamide as a chiral auxiliary for the asymmetric synthesis of α-alkylated amines (see Scheme 1.3.3a).[21] Immobilisation of enantiopure sulfinamide fragment **49** was achieved *via* hydroboration of the alkene moiety and Suzuki coupling of the resulting boronic acid onto bromo-polystyrene resin. Complexation of aldehydes with $Ti(OEt)_4$ as a Lewis acid, with subsequent addition of ethylmagnesium bromide, afforded α-branched amines **51** which were then cleaved as their hydrochloride salts by treatment with HCl in a mixed DCM / *n*-BuOH solvent. Chiral products **52** were obtained in near quantitative yield (90 – 95%) based on the calculated loading of the auxiliary fragment onto the resin (although this value was not disclosed) and high ee (74 – 94%). However, it should be noted that the stereochemistry of the polymer-supported auxiliary **53** is destroyed in the product cleavage step, so the polymer-supported chiral auxiliary could not be readily recycled for subsequent asymmetric reactions.



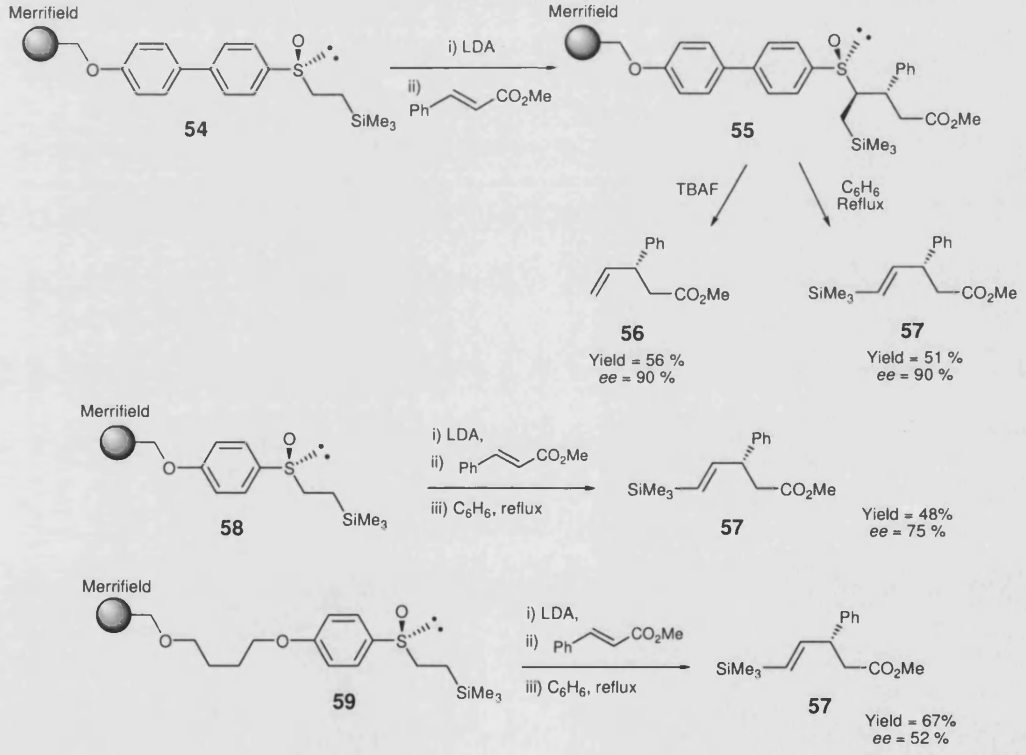
Scheme 1.3.3a: *Immobilisation of an enantiopure sulfinamide* **49** *onto solid support and application of the resulting resin* **50** *as a chiral auxiliary for asymmetric synthesis of α-alkylated amines* **52** *(as HCl salts), as described by Ellman et al.*

Toru *et al.* reported the asymmetric conjugate addition of resin-bound chiral β-(trimethylsilyl)ethyl sulfoxide **54** to α,β-unsaturated carbonyl compounds (see Scheme 1.3.3b).[22] Resin bound sulfoxide **54** was treated with LDA at -78 °C and methyl cinnamate added. Cleavage of functionalised resin **55** was achieved by heating in benzene to afford methyl-3-phenyl-5-trimethylsilylpent-4-enoate **57** in 51% yield and 90% *ee*. The presence

of the β-silyl group both accelerated elimination of the resin-bound sulfoxide fragment and controlled the regioselective formation of the double bond of **57**. Alternatively, treatment of the resin **55** with TBAF caused desilylsulfinylation to afford the vinyl analogue **56** in 56% yield and 90% *ee*.

The stereoselectivity of the conjugate addition reaction was found to be dependant on the nature of the spacer. Reaction of the analogous phenyl spacer resin **58** under the same conditions afforded **57** in similar yield but a significantly lower ee of 75%, whereas the inclusion of a highly flexible alkyl chain spacer in resin **59** reduced the ee of **57** even further to just 52%.

Again, it should be noted that the cleavage of the product from the resin destroys the chirality of the polymer-bound sulfoxide moiety and therefore it is not possible to directly recycle this auxiliary.



Scheme 1.3.3b: *Toru's polymer-bound chiral sulfoxide auxiliary in asymmetric conjugate addition reactions.*

1.3.4 Oxazolidin-2-one auxiliaries

By far the most common chiral auxiliary to be immobilised onto polymer support is the Evans oxazolidin-2-one. This is due to its immense popularity in solution phase synthesis that stems from the excellent levels of stereoselectivity observed in a wide variety of asymmetric reactions involving enolate intermediates.

Two different types of polymer supported oxazolidin-2-ones have been employed for asymmetric synthesis to date. These polymers are derived from either serine or tyrosine to create polymer-supported oxazolidin-2-ones **60** and **2** respectively, where the chiral auxiliary is attached to the polymer support *via* either their primary alcohol or phenolic functionalities respectively.

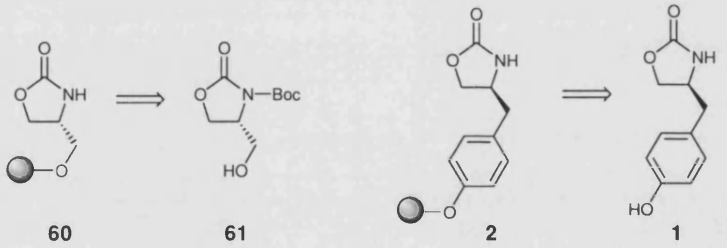
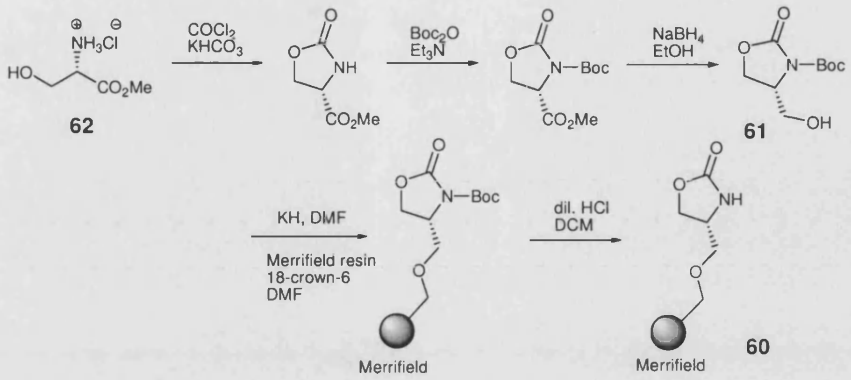


Fig 1.3.4a: *Polymer-supported serine-derived* (**61**) *and tyrosine-derived* (**2**) *oxazolidin-2-ones and their retrosynthetic analysis.*

The remainder of this chapter reviews the synthesis and applications of polymer-supported oxazolidin-2-one derived auxiliaries reported to date, which illustrate the significant problems associated with the transferral of standard reaction conditions of oxazolidin-2-ones from solution to solid phase.

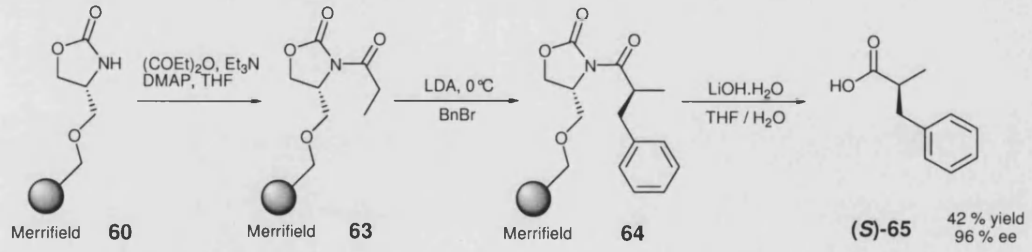
Serine derived polymer-supported oxazolidin-2-ones

The first report on the synthesis and application of a polymer-supported Evans oxazolidinone was published in 1996 by Allin and Shuttleworth, see Scheme 1.3.4a.[23]



Scheme 1.3.4a: *Reported synthesis of serine-derived oxazolidin-2-one* **61** *and its subsequent immobilisation onto solid phase.*

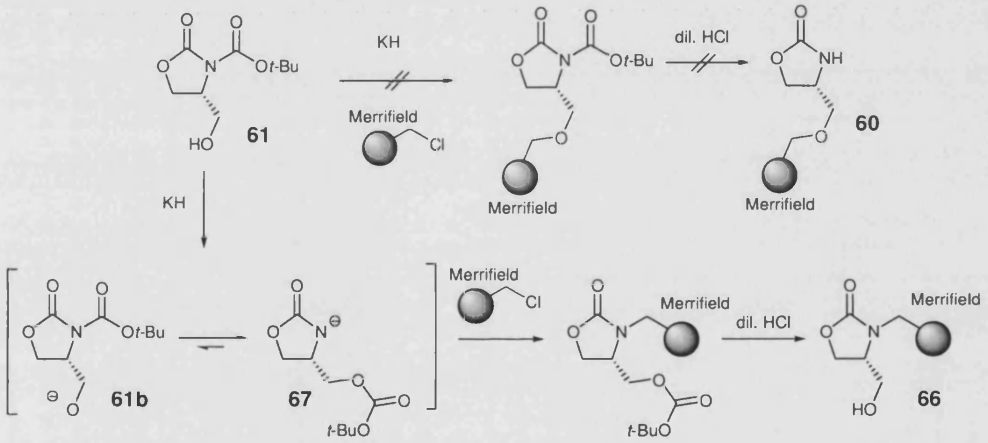
Treatment of commercially available L-serine methyl ester hydrochloride **62** with phosgene, [24] followed by *N*-Boc-protection of the oxazolidin-2-one nitrogen and reduction of the ester moiety afforded oxazolidin-2-one **61** (see Scheme 1.3.4a). It was reported that this oxazolidin-2-one fragment **61** was immobilised onto polymer support *via* its hydroxyl group, with subsequent deprotection to give polymer-bound *N*-H oxazolidin-2-one **60**. It was further claimed that polymer-supported oxazolidin-2-one **60** was acylated with propionic anhydride under basic conditions to give *N*-propionyl-oxazolidin-2-one **63.** This species then underwent an asymmetric enolate alkylation reaction involving treatment with LDA and electrophilic quenching with benzyl bromide. Basic hydrolysis of the resultant resin **64** was reported to afford (*S*)-2-benzyl-propionic acid (***S*)-65** in 42% overall yield and excellent enantioselectivity (*ee* = 96%) (see Scheme 1.3.4b).



Scheme 1.3.4b: *Reported acylation and asymmetric enolate alkylation reaction of polymer-supported oxazolidin-2-one* **60**, *as described by Allin and Shuttleworth.*

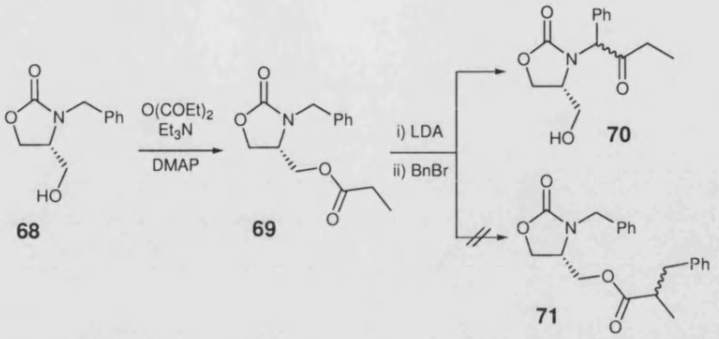
However, the validity of this scheme was subsequently questioned by two other groups.[25,26] Bew *et al.* [26] conducted studies that indicated that the material described as the *O*-bound polymeric auxiliary **60** was in fact *N*-bound polymeric auxiliary **66**, (see Scheme 1.3.4c).

This was attributed to a facile *N-O* acyl exocyclic rearrangement that had occurred as the auxiliary was immobilised onto Merrifield resin.[27] It was shown that upon deprotonation of the alcohol functionality of *N*-Boc-oxazolidin-2-one **61**, the resulting alkoxide species **61b** underwent intramolecular attack at the *N*-Boc-carbonyl, resulting in the transferral of the Boc group from the nitrogen atom to the oxygen atom to form *O*-Boc-oxazolidin-2-one **67**. Subsequent treatment of the *N*-anion with chloromethyl polystyrene (i.e. Merrifield resin) would then result in immobilisation of the oxazolidin-2-one fragment **67** *via* its nitrogen atom and not *via* the oxygen as originally reported by Allin and Shuttleworth. The resulting polymer-bound species after Boc-deprotection was therefore *N*-bound oxazolidin-2-one **66** and not *O*-bound oxazolidin-2-one **60**.



Scheme 1.3.4c: *N,O-Boc-exocyclic rearrangement of N-Boc,O-H oxazolidin-2-one* **61** *under conditions employed for immobilisation onto Merrifield resin resulting in immobilisation via its nitrogen atom, not its oxygen atom as reported.*

The occurrence of this rearrangement was confirmed by solution phase studies in which the chloromethyl polystyrene was replaced with benzyl bromide, thus producing *N*-benzyl-*O*-H-oxazolidin-2-one **68**. Importantly, it was then shown that acylation of solution phase *N*-benzyl-*O*-H oxazolidin-2-one **68** with propionic anhydride and use of the resulting species **69** for the asymmetric alkylation reaction using LDA and benzyl bromide did not produce any trace of the α-benzylated-propionyl oxazolidin-2-one **71**, with only rearranged ketones **70** being produced in low yield (see Scheme 1.3.4d).[28] It is therefore unclear how (*S*)-2-benzylated propionic acid (***S*)-65** could have been prepared from basic hydrolysis of the corresponding solid-phase analogue as originally reported.



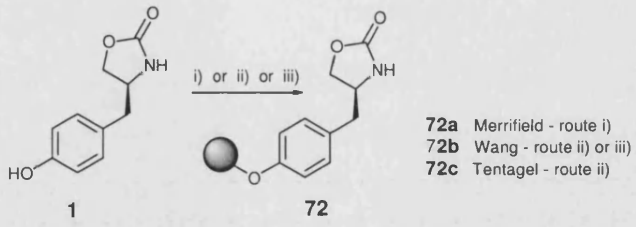
Scheme 1.3.4d: *Attempted asymmetric α-alkylation of N-benzyl,O-propionyl oxazolidin-2-one* **69**.

Upon re-examination of their previous claims, Allin and co-workers confirmed the structure of the polymer-bound species as *N*-bound oxazolidin-2-one **66** *via* magic-angle NMR and recently withdrew their previous claims of success in this area.[29]

No further examples of serine-derived auxiliaries have since been published, with all subsequent auxiliaries being synthesised from tyrosine.

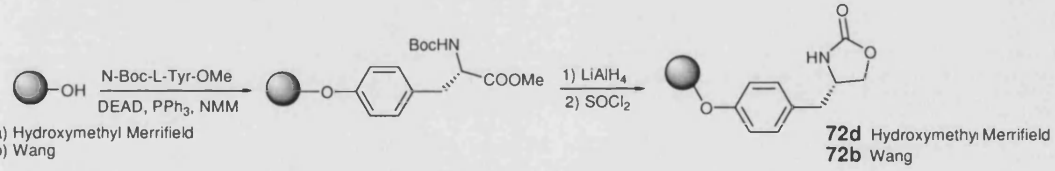
Synthesis of tyrosine-derived polymer-supported oxazolidin-2-ones.

To date, with just one exception, the strategy employed for preparation of polymer-supported Evans oxazolidin-2-ones has involved synthesis of (*S*)-4-(4-hydroxybenzyl)-oxazolidin-2-one **1** in solution phase with attachment to the resin as a final step. Three types of resin have been used - Merrifield, Wang and less frequently Tentagel.[25] Attachment to Merrifield resin has been achieved *via* nucleophilic substitution reactions, with Burgess preparing an *N*-acylated oxazolidin-2-one resin using the phenolate anion of the auxiliary to displace chloride from chlorobenzyl Merrifield resin under relatively harsh conditions (see Scheme 1.3.4e). Attachment to Wang resin (and Tentagel) has been achieved using Mitsunobu coupling under generally milder conditions.



Scheme 1.3.4e: *Reagents and conditions: i) $^{t}BuOK$, cat. 18-crown-6 / Bu_4NI, DMF, 75 °C, 84 h, 30% loading; ii) EtO_2CNNCO_2Et, PPh_3, 20 h, loading: 56% Wang, 60% Tentagel; iii) EtO_2CNNCO_2Et, PPh_3, THF, 0 °C 1 h then 25 °C, 72 h, loading 0.79 mmol/g.*

An alternative strategy was employed by Winkler *et al.* who described the assembly of the oxazolidinone 'on bead' using similar chemistry to that employed previously for solution phase synthesis.[30] The commercially available methyl ester of *N*-Boc-L-tyrosine was attached to the resin (hydroxymethyl Merrifield and Wang) *via* a Mitsonubu coupling. Reduction of the ester to the alcohol using $LiAlH_4$, and subsequent cyclisation of the resulting alkoxide onto the *N*-Boc protecting group afforded the polymer-bound oxazolidin-2-one **72** according to scheme 1.3.4f.

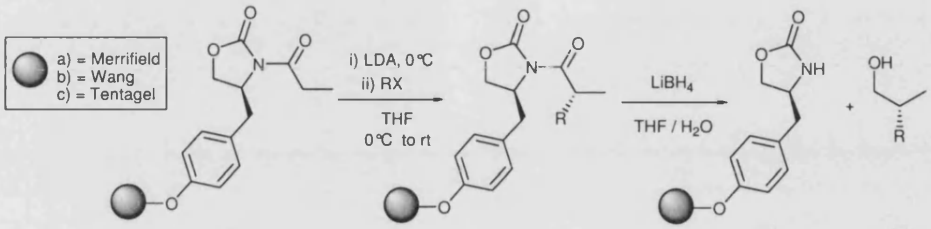


Scheme 1.3.4f: *Assembly of oxazolidin-2-one 'on-bead', as described by Winkler and co-workers.*

Applications of solid-supported oxazolidin-2-ones

Burgess and Lim investigated the asymmetric α-alkylation of a solid-supported oxazolidin-2-one **72**, (see scheme 1.3.4g).[25] Hence *N*-propionyl oxazolidin-2-one **73** was enolised with LDA then alkylated with benzyl bromide before $LiBH_4$ cleavage to yield the chiral product as alcohol **(*R*)-65**. Their report primarily focused on the differences in reactivity and selectivity that were found when the nature of the polymer support (Wang, Merrifield or Tentagel) was changed. Wang resin was found to be the preferred support in terms of both yield and selectivity. However, irrespective of the resin used, in each case the yield and ee of the alcohol product formed were found to deteriorate with reaction time, a feature not

previously reported in solution phase. No explanations were offered for the deterioration in *ee*, although its loss was noted to be related to the number of equivalents of base used. It was tentatively suggested that the decrease in yield could be due to "loss of the propionyl group from the oxazolidin-2-one prior to cleavage".



Scheme 1.3.4g: *Asymmetric α-alkylation of polymer-supported N–propionyl-oxazolidin-2-one* **73** *reported by Burgess and Lim.*

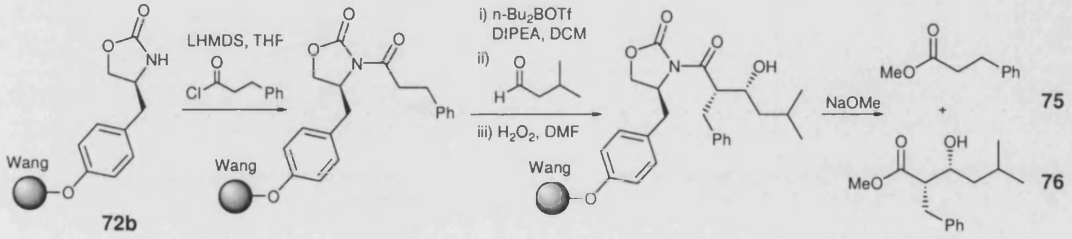
Entry	Alkylating agent R-X	Equiv. LDA	Reaction conditions [a] Time at 0 °C (h) [b]	Time at 25 °C (h) [c]	Yield of **74** (%)	*ee* of **74** (%)
1	BnBr	3	0.5	0.33	66	90
2	BnBr	2	1.0	12	39	86
3	CH_2CHCH_2Br	3	0.5	0.33	25	81
4	CH_2CHCH_2Br	2	2.0	15	-	88
5	$BnOCH_2Cl$	3	0.5	0.33	12	71
6	$BnOCH_2Cl$	2	2.5	14	20	76

Table 1.3.4a: *Optimisation of reaction conditions using Wang resin- supported oxazolidin-2-one* **72b**. [a] *Polymer-supported* **73b** *in THF at 0 °C treated with LDA for 30 min.* [b] *Specified alkylating agent added and reaction stirred at 0 °C for stated period of time,* [c] *Warmed to 25 °C for stated period of time*

Conditions were optimised for benzyl bromide as the alkylating agent which gave **(*R*)-65** in a respectable 66% yield and 90% ee (see Table 1.3.4a, entry 1). However, when the same reaction conditions were applied to other electrophiles (See Table 1.3.4a, entries 3-6), poor yields were gained implying that each reaction would require individual optimisation.

Purandare *et al.* demonstrated the first use of solid supported oxazolidin-2-one **72b** (Wang resin) for the synthesis of chiral α-substituted β-hydroxyacid derivative **76** *via* an aldol condensation reaction (see Scheme 1.3.4h).[31] The polymer bound auxiliary **72b** was *N*-acylated with hydrocinnamoyl chloride and its aldol reaction with isovaleraldehyde investigated under varying conditions *i.e.* variation of reaction temperature, number of equivalents of boron reagent and Hünig's base (see Table 1.3.4b). It was found that

repeated treatment of the resin with each reagent (with removal of excess reagent and washing with DCM between treatments) gave the greatest conversions of starting material to product. Under optimised reaction conditions ester **76** was obtained along with hydrocinnamoyl ester **75** (derived from un-reacted starting material) in a 90:10 ratio after cleavage from the polymer support using sodium methoxide in THF. HPLC and ^{1}H-NMR revealed that the product was predominantly a single *syn* diastereomer (20:1), but no isolated chemical yield of cleaved ester product **76** was given.



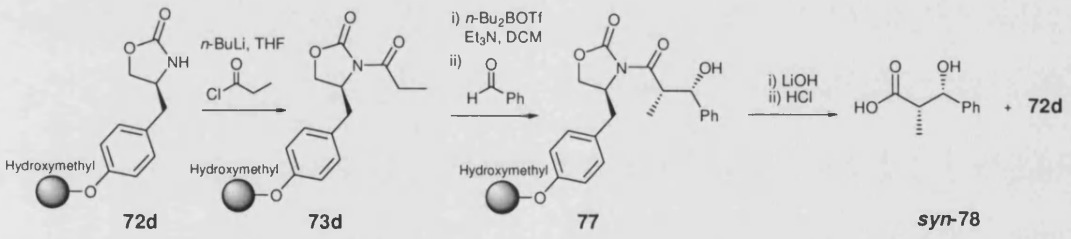
Scheme 1.3.4h: *Asymmetric aldol reaction of polymer-supported N-hydrocinnamoyl-oxazolidin-2-one with isovaleraldehyde as reported by Purandare et al.*

Entry	Equiv. of Bu_2BOTf	Equiv. of Hunig Base	Equiv. of aldehyde	Reaction temp (°C)	Ratio **76**:**75**
1	2.0	2.0	4.0	-78	15:85
2	2.0	2.0	4.0	-20	60:40
3	4.0	4.0	8.0	-20	50:50
4	2 x 2.0 *	2 x 2.0 *	4.0	-20	90:10

Table 1.3.4b: *Optimisation of reaction conditions for aldol reaction of N-acylated oxazolidin-2-one derivative with isovaleraldehyde. * Indicates multiple treatments. Resin treated with reagent, washed three times with anhydrous DCM, then treated with 2nd batch of reagent.*

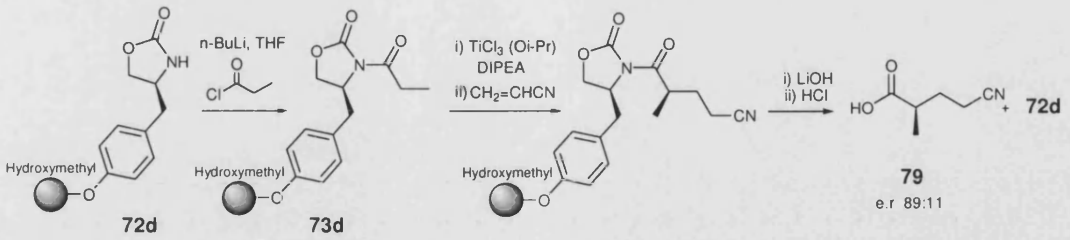
Phoon *et al.* also reported the use of solid supported auxiliary **72d** in various aldol reactions (see Scheme 1.3.4j) and achieved yields and enantioselectivity comparable to the corresponding reactions in solution phase.[32] However severe problems were noted in transferral of experimental conditions from solution to solid phase, and the need for flexible experimental design was highlighted. Despite the well-known advantage of solid-phase chemistry providing the option to use an excess of soluble reagents to drive reactions to completion, this was reported not to be feasible in this case.[33] It was reported that in this situation a reversal of stereochemistry was observed when two equivalents of *n*-

dibutylboron triflate were employed. To circumvent such issues, the formation of the enolate was first driven to completion using an excess of *n*-dibutylboron triflate (13 equivalents) and triethylamine, with the excess reagents then being washed away. Again, a strategy involving multiple treatments of resin with reagents (with draining and rinsing in between), was employed. Thereafter, the resin was re-suspended in dichloromethane and cooled to –78 °C before benzaldehyde was added to form resin-bound product **77**. Additionally the cleavage of the aldol product from polymer support proved problematic. The standard conditions used in solution phase reactions (lithium hydroperoxide) resulted in the product being "heavily contaminated with unidentifiable impurities" which appeared to originate from destruction of the resin. Consequently, cleavage was carried out using lithium hydroxide in THF, which produced a cleaner cleavage product ***syn*-78**, however with the possibility of partial endocyclic cleavage of the polymer supported auxiliary having occurred. The *syn* diastereomer of the acid product was formed with a diasteromeric excess of greater than 98% and in 63% chemical yield overall (based on loading of chiral auxiliary on resin).



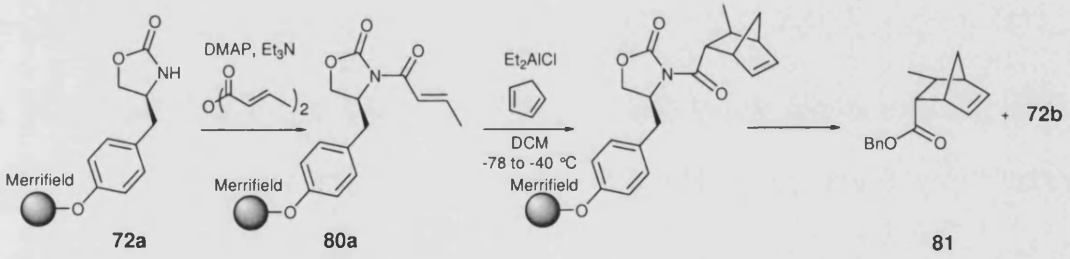
Scheme 1.3.4j: *Asymmetric aldol reaction of polymer-supported N-propionyl-oxazolidin-2-one* **73d** *with benzaldehyde as reported by Phoon et al.*

Phoon *et al* also explored the use of *N*-propionylated Evan's chiral auxiliary **73d** for asymmetric conjugate addition on solid phase (see Scheme 1.3.4k).[32] α-methylated 3-cyano butyric acid **79** was found to be the major product, being formed in an enantiomeric ratio of 89:11 and 52% overall yield (based on loading of chiral auxiliary on resin). In the corresponding solution phase reaction, the enantiomeric ratio is reported to be 98:2,[34] hence in this case, the polymer-supported version results in a decrease in stereoselectivity.



Scheme 1.3.4k: *First example of asymmetric conjugate addition on polymer support, as reported by Phoon et al.*

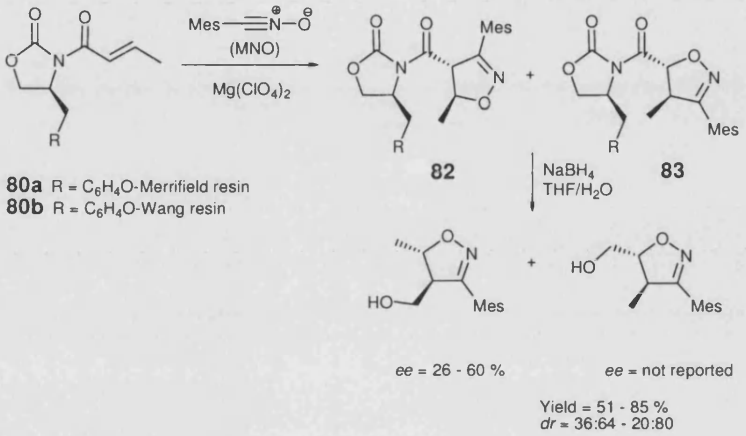
Winkler *et al.* investigated the use of polymer-supported *N*-crotonyl-oxazolidinones **80a** (on Merrifield resin) and **80b** (on Wang resin) in Diels Alder cycloaddition reactions (see Scheme 1.3.4m).[30] The attempted Lewis acid catalysed Diels Alder reaction between cyclopentadiene and Wang supported *N*-crotonyl oxazolidinone **80b** at low temperature did not lead to any desired reaction presumably due to the instability of the Wang resin to Et_2AlCl. The Merrifield resin **80a** proved more robust to the Lewis acidic conditions and the desired reaction proceeded to form **81** in 26% overall yield (including synthesis of polymer-bound auxiliary) and in 86% *ee*, (endo/exo ratio of 21:1). These results are comparable to the solution-phase counterpart, which yielded **81** in 42% yield (not including auxiliary synthesis) and 88% *ee*.



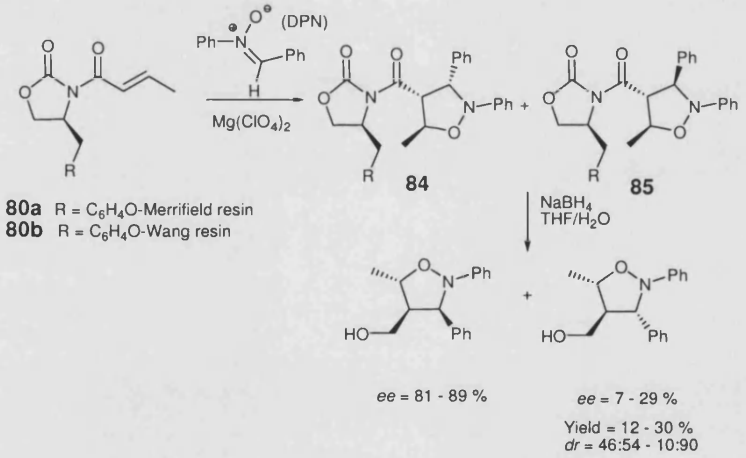
Scheme 1.3.4m: *Diels Alder cycloaddition of cyclopentadiene and polymer-supported N-crotonyl-oxazolidin-2-one* **80a**, *as reported by Winkler et al.*

Faita and Quadrelli reported the use of a resin-bound Evans' auxiliaries **80a,b** for 1,3-dipolar cycloaddition reactions with either mesitonitrile oxide (MNO) or diphenylnitrone (DPN) as 1,3-dipoles (see schemes 1.3.4n and 1.3.4p), [35, 36] to form isomeric cycloadducts **82** and **83** (for MNO) and **84** and **85** (for DNP). The products were subsequently released from the resin *via* $NaBH_4$ cleavage. Generally the reactions with mesitonitrile were more successful than those with diphenylnitrone, the latter being sluggish and affording low

yields of the desired products. In all cases, the reactions on solid support (both Merrifield and Wang) were inferior to those performed in solution phase, both in terms of yield and stereoselectivity. The polymer support was shown to interfere significantly with the action of the magnesium catalyst and in some cases resulted in reversal of the stereocontrol, both in terms of regio- and enantio-selectivity.



Scheme 1.3.4n: *Asymmetric 1,3-dipolar cycloaddition of polymer-supported N-crotonyl oxazolidin-2-ones* **80a/b** *with mesonitrile oxide (MNO) as the 1,3-dipolar species.*

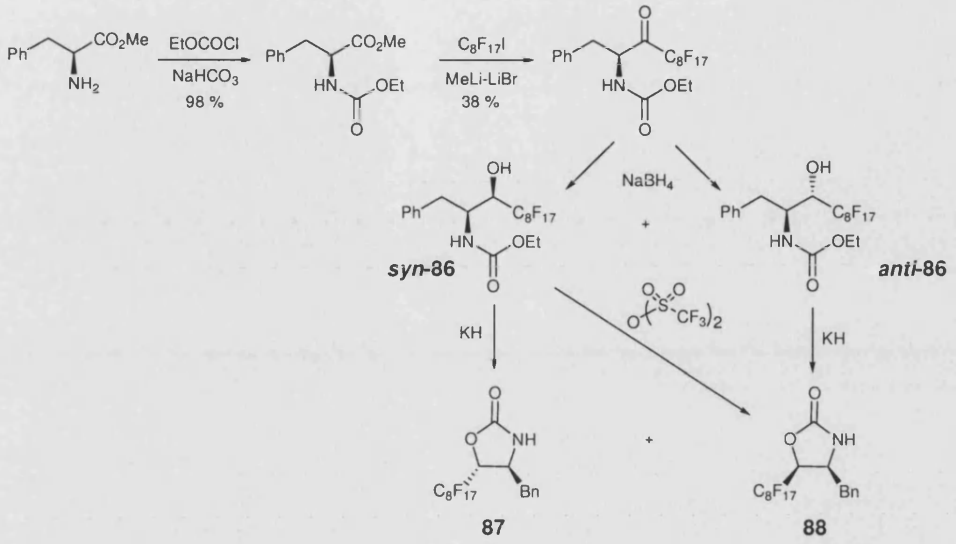


Scheme 1.3.4p: *Asymmetric 1,3-dipolar cycloaddition of polymer-supported N-crotonyl oxazolidin-2-ones* **80a/b** *with diphenylnitrone (DPN) as the 1,3-dipolar species.*

Overall, this study highlighted the sensitivity of solid-supported auxiliaries and the ensuing asymmetric reaction to the nature of the solid support. With reduced (and seemingly unpredictable) yields and enantioselectivities relative to the solution phase analogue and

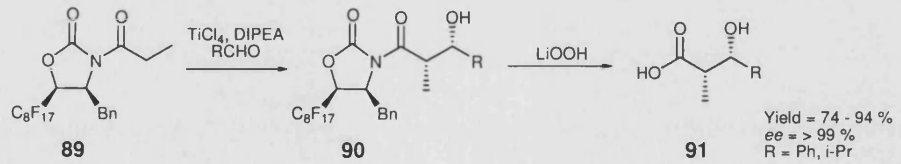
extremely long reaction times (minimum four days), these protocols were inferior to existing solution phase reactions. The authors later reported the use of a soluble polymer (non-cross-linked polystyrene) to support the oxazolidin-2-one and its use in cycloaddition reactions.[37] This soluble polymer helped to alleviate many of the problems of the solid phase system, and resulted in faster reaction rates and more efficient complexations between the metal catalysts and co-ordinating substrates. However, the results obtained were still inferior compared to the solution phase version.

Fluorous synthetic methodologies are similar to polymer-supported synthesis techniques in that the physical properties of the fluorine-containing product are used to simplify product purification.[38] In this regard, a fluorous version of an oxazolidin-2-one auxiliary has been reported by Hein and Hultin and used in asymmetric aldol [39] and 1,3-dipolar cycloaddition reactions (see Scheme 1.3.4q).[40] Fluorous oxazolidin-2-ones **87** and **88** were prepared from L-phenylalanine methyl ester in poor yield due to several issues arising from the presence of the fluorous group. Firstly, the reaction of the ester with the fluoroalkyllithium species was low yielding due to the latter reagents' instability, even when formed *in-situ*. Furthermore, attempts to acheive diasteroselective reduction of the resulting ketone resulted in mixtures of the *syn-* and *anti-* alcohols ***syn*-86** and ***anti*-86** respectively. This is presumably a consequence of the electron-withdrawing nature of the perfluoroalkyl chain which reduces the Lewis basicity of the fluoroketone and hence alters the transition state of the subsequent reduction reaction. The ketone was therefore simply reduced with $NaBH_4$ with chromotographic separation of the two resulting diastereomers. However, unwanted *syn*-alcohol ***syn*-86** could be converted directly into desired oxazolidin-2-one **88** by treatment with triflic anhydride, which caused cyclisation with inversion of the secondary alcohol centre. Recently, an improved synthesis of fluorous oxazolidin-2-ones addressing these issues has been reported.[41]



Scheme 1.3.4q: *Synthesis of fluorous oxazolidin-2-one* **88** *from (L)-phenylalanine methyl ester, as reported by Hein and Hultin.*

The *syn-N*-propionyl fluorous oxazolidin-2-one **89** was converted to its titanium enolate *via* treatment with $TiCl_4$ and DIPEA, then reacted with several aldehydes (see Scheme 1.3.4r). After hydrolysis, the *syn*-hydroxy acids **91** were isolated in 74 - 94% yield with greater than 99% ee, comparable to the results gained from the analogous solution phase version using classical Evans oxazolidin-2-one auxiliaries. The use of fluorous auxiliary **88** allowed the products to be easily and rapidly purified *via* fluorous solid phase extraction (FSPE). The crude reaction mixtures **90** were evaporated and the residues dissolved in *n*-propanol and passed down a column charged with perfluoroalkyl-modified silica gel. Washing with a fluorophobic solvent mixture (e.g. 3:7 water:*n*-propanol) rapidly stripped all organic and inorganic materials from the column. THF or acetone then eluted the fluorous products in excellent yield and purity.



Scheme 1.3.4r: *Asymmetric aldol reaction employing fluorous oxazolidin-2-one* **89**, *as reported by Hein and Hultin.*

The authors claim this fluorous oxazolidin-2-one **88** represents an ideal combination of the benefits of solution and solid phase supports. Like solid supported auxiliaries, the physical properties of the fluorous oxazolidin-2-one allows facile purification of reaction products. However, ultimately, the fluorous oxazolidin-2-one remains a solution-phase auxiliary and hence retains many of the inherent advantages including compatibility with classical enolate reaction conditions, conventional characterisation, and the option to conduct purification (*e.g.* separation of diastereomers) if required.

1.4 Conclusions

This brief literature review has demonstrated that efficient asymmetric synthesis using a polymer-supported chiral auxiliary is possible. Occasionally, the reaction conditions for the analogous solution phase reaction can be directly transferred successfully to the solid phase reaction. However, in most cases, reaction conditions need to be re-optimised for application to solid phase systems since the presence of the polymer support can have a significant effect on the reactivity and stereoselectivity of the chiral auxiliary fragment. In some cases, this effect can be beneficial, for example, both Kawana[3] and Schore[4] developed polymer-supported chiral auxiliaries which gave products of highereethan the corresponding solution phase reaction.

Some key points of the literature review are summarised below.

- A variety of different chiral auxiliaries have been immobilised on polymer support, however many more remain to be investigated.
- There has not been much variety in the choice of polymer support used for immobilisation. In the vast majority of cases, commercially available cross-linked polystyrene supports have been employed, however, some success has been achieved with non-crosslinked soluble polystyrene supports and the emerging fluorous support.

- In an attempt to minimise steric interactions between the polymer support and the chiral auxiliary, some groups have incorporated a linker molecule between the two components.
- The inclusion of an orthogonal cleavage strategy within the linker or chiral auxiliary fragment allows for easy characterisation of polymer-supported intermediates *via* selective cleavage and solution-phase characterisation.
- Large excesses of reagents are often not essential but can be useful to drive polymer-supported asymmetric reactions to completion. Alternatively, multiple treatments of resins with reagents (with filtration between each treatment) has also shown some utility.
- Isolated yields of products are often significantly lower than the corresponding solution phase reactions, but rarely have explanations been given for this reduction.
- It has been shown that in some cases, the polymer supported chiral auxiliary can be recycled with little loss in yield and / or stereoselectivity.

Chapter 2 Synthesis of chiral N-Acyl-oxazolidin-2-ones and their use in preliminary solution phase asymmetric reactions.

2.1 Selection of chiral auxiliary for solid-supported system

A solid supported oxazolidin-2-one chiral auxiliary requires three main components: a polymer support, a chiral auxiliary unit and a suitable linker to attach the two fragments together (see Fig. 2.1a).

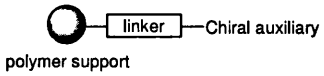
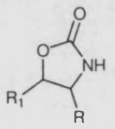


Fig 2.1a: *Essential components of a solid supported chiral auxiliary.*

As reviewed in the preceding chapter, a variety of different chiral auxiliaries have been immobilised onto solid support over the years, including carbohydrate-based auxiliaries, chiral amines and sulfoxides (for recent review see reference 7). However, the most common chiral auxiliary to be immobilised has been the Evans oxazolidin-2-one auxiliary, because of its efficiency, versatility and popularity in solution phase asymmetric synthesis. The parent auxiliaries **100** are available as both enantiomers in two high yielding steps from inexpensive α-amino acid starting materials (see Fig 2.1b).



100

R = ^{i}Pr (valine)
R = Bn (phenylalanine)
R = Ph (and R_1 = Me) (norephedrine)
(unless otherwise stated, R_1 = H)

Fig. 2.1b: *Common examples of Evans-type oxazolidin-2-one auxiliaries*

A representative asymmetric reaction cycle employing an oxazolidin-2-one auxiliary is portrayed in Figure 2.1c. The attachment of the auxiliary to the substrate is generally achieved *via* an *N*-acylation reaction employing an acid chloride, anhydride or carboxylic acid which ensures applicability to a wide variety of substrates. Once constructed the *N*-acyl oxazolidin-2-one is highly versatile and has been shown to provide excellent levels of diastereoselectivity in a wide variety of reactions including enolate alkylations, Michael additions, aldol condensations, Diels Alder cycloadditions and 1,3-dipolar cycloadditions. It has also been found that any diastereomeric products formed are generally easy to separate *via* column chromatography or recrystallisation. The oxazolidin-2-one auxiliary can then be easily cleaved by a variety of nucleophiles (allowing for the introduction of a further point of diversity) to afford enantiopure products and the intact, robust chiral auxiliary that can be recycled as required.

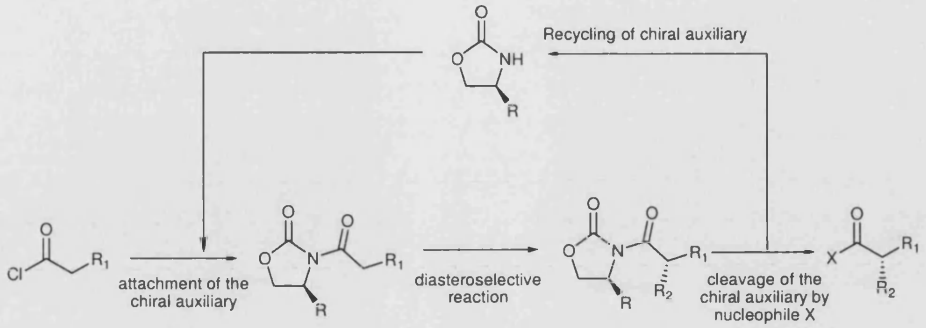
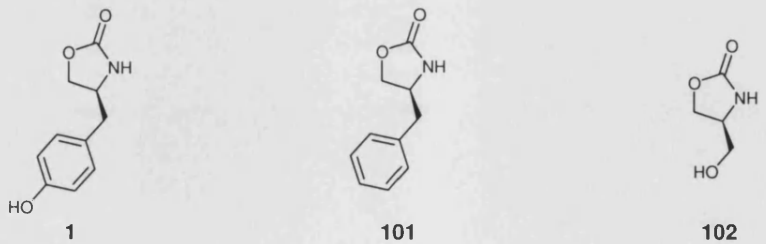


Fig. 2.1c: *Representative asymmetric synthesis using an oxazolidin-2-one chiral auxiliary*

Given the fact that the oxazolidin-2-one chiral auxiliaries have proven remarkably efficient, versatile and popular for solution phase synthesis, and that they have also been employed with some success in previous solid phase systems, it was decided to employ an oxazolidin-2-one fragment as the chiral auxiliary in our solid-supported reactions. The strategy chosen for selection of the polymer support and linker are discussed in the following chapter.

A review of the published accounts of solid-supported oxazolidin-2-ones revealed two common features.

1) The most popular oxazolidin-2-one fragment for immobilisation is (*S*)-4-(4-hydroxybenzyl)-oxazolidin-2-one **1** derived from L-tyrosine, (see Fig 2.1d). This fragment is sterically and electronically similar to the commonly used solution phase auxiliary (*S*)-4-benzyloxazolidin-2-one **101** yet the presence of the phenol moiety allows attachment to a variety of different linkers. As described, the serine-derived (*S*)-4-(hydroxymethyl)oxazolidin-2-one **102** has been shown to be unsuitable for immobilisation onto polymer support (for details see Chapter 1).[29]



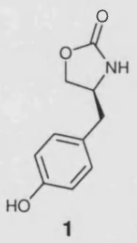
1 **101** **102**

Fig 2.1d: *Examples of Evans oxazolidin-2-one auxiliary fragments,* **1** *and* **102** *previously proposed for immobilisation onto polymer support.*

2) To date, with just one exception,[30] the preparation of solid-supported oxazolidin-2-ones has involved construction of the oxazolidin-2-one fragment in solution phase with subsequent immobilisation onto the solid support. This appeared to be the simplest and most reliable route as solution phase intermediates are easily characterised *via* conventional methods unlike their solid phase counterparts.

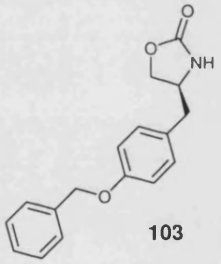
2.2 Synthesis of chiral auxiliaries

In this section, the syntheses of three oxazolidin-2-one chiral auxiliary fragments are described. Oxazolidin-2-one **1** was needed for immobilisation onto resin and subsequent solid supported reactions whilst oxazolidin-2-ones **103** and **101** were required to conduct preliminary solution phase studies (see Fig 2.2a). The two solution phase auxiliaries were deemed necessary in order to carry out a full investigation into analogous solution phase asymmetric reactions before commencing development of solid phase variants.



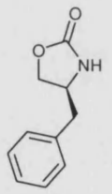
1

(*S*)-4-(4-hydroxybenzyl)oxazolidin-2-one



103

(*S*)-4-(4-(benzyloxy)benzyl)oxazolidin-2-one



101

(*S*)-4-benzyloxazolidin-2-one

Fig 2.2a: *Oxazolidin-2-one auxiliaries to be prepared and used in this study.*

Benzyloxybenzyl-oxazolidin-2-one **103** was intended to be a solution phase mimic of the forthcoming solid phase system with the *O*-benzyl group mimicking the polystyrene support. However, its use as a chiral auxiliary had not been reported previously so the commonly used oxazolidin-2-one auxiliary **101** (from L-phenylalanine) was also prepared in parallel to ensure that the performance of **103** would conform to the high standards typical of an Evans oxazolidin-2-one. These solution phase reactions would serve to identify any features of solution phase reactions that might be relevant to its transferral to

solid support *e.g.* any unwanted by-products formed. The results gained would also allow direct comparison between traditional solution phase routes and any new solid-phase methods developed.

2.2.1 Synthesis of (S)-4-(4-benzyloxybenzyl)-oxazolidin-2-one (103) *and (S)-4-(4-hydroxybenzyl)oxazolidin-2-one* (1). [42]

We required a synthesis of (*S*)-4-(4-hydroxybenzyl)-oxazolidin-2-one **1** that was both high yielding and amenable to scale up. A review of the literature revealed that five routes (**A-E**) to **1** had been reported previously, the details of which are described in Scheme 2.2.1a.

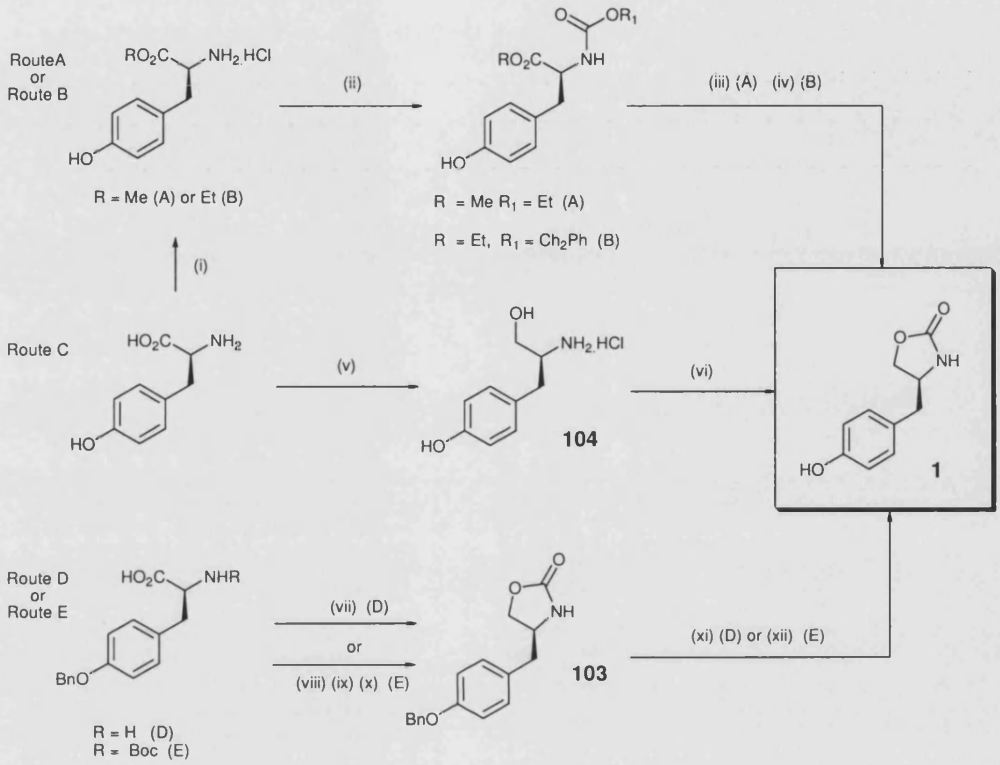
Routes **A** [35] and **B** [43] involved a strategy in which the carboxylate and amino groups of L-tyrosine were protected as an ester and carbamate respectively. Subsequent reduction of the ester group with $NaBH_4$ afforded an alkoxide that underwent intramolecular cyclisation onto the carbonyl of the carbamate protecting group yielding oxazolidin-2-one **1**. Faita *et al.* (route **A**) [35] employed a two step reduction / thermal cyclisation procedure whereas Sudharshan *et al.* (route **B**) [43] developed a 'one-pot' operation to affect this transformation employing LiI to facilitate cyclisation *in situ*.

Route **C** (described by Phoon *et al.*) [32] was the shortest approach employing a variation of Evans' original conditions [44] involving borane mediated reduction of the acid functionality of L-tyrosine to afford L-tyrosinol **104** that was then converted to oxazolidin-2-one **1** *via* treatment with diethyl carbonate under basic conditions.

The synthesis of Purandare *et al.* (route D) [31] commenced from commercially available *O*-Benzyl-L-tyrosine and proceeded *via* reduction of the carboxylate to the corresponding alcohol by treatment with $LiAlH_4$, followed by treatment with phosgene to afford an *O*-benzyl oxazolidin-2-one **103** that was deprotected to give **1** *via* hydrogenolysis.

Finally, in route **E** Burgess *et al.* [25] employed *O*-benzyl-*N*-Boc-L-tyrosine as the starting material that was reduced to its *N*-Boc-amino-alcohol, followed by *N*-Boc deprotection and

treatment of the resulting amino alcohol with phosgene to afford an *O*-benzyl oxazolidin-2-one **103** that was once again deprotected to **1** under hydrogenolytic conditions.

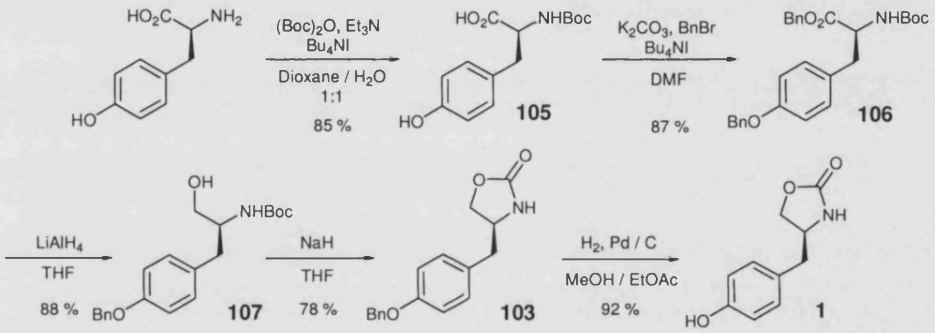


Scheme 2.2.1a: *Literature routes for preparation of (S)-4-(4-hydroxybenzyl)-oxazolidin-2-one* **1**.

Reagents and conditions: ***(i)*** *$SOCl_2$, MeOH, 95%, (**A**); or EtOH, HCl, (**B**),* ***(ii)*** *(a) K_2CO_3, (b) EtOCOCl, $NaHCO_3$, 95%, (**A**); or BnOCOCl, Na_2CO_3 (aq), $CHCl_3$, (**B**);* ***(iii)*** *(a) $NaBH_4$, THF, Δ, 82%, (**A**); (b) K_2CO_3, toluene, Δ, 50%, (**A**);* ***(iv)*** *$NaBH_4$, LiI, THF, Δ, 90%, (**B**);* ***(v)*** *(a) $BH_3.SMe_2$, $BF_3.OEt_2$, THF, Δ; (b) 5M NaOH(aq.), Δ; (c) 6M HCl(aq), 83% (three steps) (**C**);* ***(vi)*** *(a) $NaHCO_3$ (aq), (b) $(EtO)_2CO$, K_2CO_3, 125 °C, 86% (two steps) (**C**);* ***(vii)*** *(a) $LiAlH_4$, THF, 60 °C; (b) $COCl_2$, toluene, 82% (two steps) (**D**);* ***(viii)*** *(a) $^iPrOCOCl$, Et_3N, THF, (**E**); (b) $NaBH_4$ (**E**);* ***(ix)*** *HCl, Et_2O-EtOAc, 25 °C, 93% (**E**);* ***(x)*** *$COCl_2$, KOH-K_2CO_3 (aq.), toluene, 0-25 °C, 98% (**E**);* ***(xi)*** *H_2, cat Pd-C, EtOH (**D**);* ***(xii)*** *H_2, cat Pd-C, MeOH-EtOAc, 25 °C, 96% (**E**).*

However, no single route appeared to fulfil all the requirements of this project. Routes **A**-**C** proceeded *via* intermediates which, due to the presence of an unprotected phenol group, had proven to be non-crystalline and highly polar leading to purification issues that reduced both yield and reproducibility.[45] Whilst these polarity problems could be overcome in routes **D** and **E** using *O*-benzyl-L-tyrosine derivatives in which the phenol group was protected as a benzyl ether, the prospect of employing highly toxic phosgene as a reagent for oxazolidin-2-one ring formation on a large scale was unattractive.

Consequently, an alternative synthesis of (*S*)-4-(4-hydroxybenzyl)oxazolidin-2-one **1** was devised that combined the relatively non-polar *O*-benzyl-L-tyrosine intermediates employed in routes **D** and **E**, with the intramolecular alkoxide/*N*-carbamate cyclisation strategy for oxazolidin-2-one ring formation used in routes **A** and **B**. This approach allowed **1** to be prepared in five steps from (L)-tyrosine, without the necessity of using phosgene as a reagent for oxazolidin-2-one ring formation (see Scheme 2.2.1b). This route also allowed the simultaneous preparation of large quantities of (*S*)-4-(4-benzyloxybenzyl)-oxazolidin-2-one **103**, that was also required as a chiral auxiliary for preliminary solution phase studies.



Scheme 2.2.1b: *Synthesis of (S)-4-(4-benzyloxybenzyl)-oxazolidin-2-one* **103** *and (S)-4-(4-hydroxybenzyl)-oxazolidin-2-one* **1**.

The first step involved protection of the primary amine of L-tyrosine with a *tert*-butoxycarbonyl (Boc) moiety. This not only prevented possible side reactions in the following steps due to the presence of an unprotected amino group but would also serve as a crucial sacrificial carbonyl donor in the oxazolidin-2-one cyclisation step. Therefore, treatment of L-tyrosine with triethylamine and di-*tert*-butyl dicarbonate in a dioxane:water (1:1 ratio) mixed solvent at room temperature according to the method of Jung,[46] afforded *N*-Boc-L-tyrosine **105** in variable yield. However, addition of tetrabutylammonium iodide as a phase transfer agent consistently increased the quantity and quality of product isolated affording **105** in 85% yield.

Protection of the phenolic hydroxyl group of **105** as a benzyl ether was necessary to ensure the ensuing cyclisation proceded in a chemoselective fashion. A benzylic ether protecting group was chosen due to the mild and selective catalytic hydrogenation conditions that could be employed for its deprotection. Also the presence of an *O*-benzyl group was reported to produce crystalline intermediates [31] which would greatly facilitate subsequent purification steps. In protecting the phenolic hydroxyl group as an *O*-benzyl ether, the carboxylic acid moiety was simultaneously protected as its benzyl ester. However this benzylic ester would be reduced in subsequent synthetic steps, so had no detrimental effect on the overall synthesis. To achieve perbenzylation, **105** was treated with K_2CO_3 and excess benzyl bromide in DMF to afford *O*-benzyl-*N*-boc-L-tyrosine benzyl ester **106** after recrystallisation in 87% overall yield.[47]

Reduction of the benzylic ester of **106** to afford the alcohol functionality necessary for the subsequent intramolecular cyclisation reaction was achieved *via* treatment with $LiAlH_4$ in THF following the method of Dondoni (THF, 0 °C to 25 °C)[48] affording (*S*)-*N*-Boc-L-tyrosinol **107** in 88% yield.

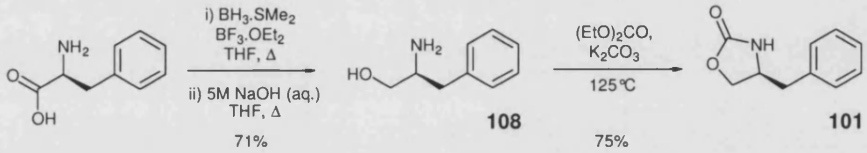
Treatment of *N*-Boc-aminoalcohol **107** with NaH in THF afforded a sodium alkoxide intermediate that underwent an intramolecular cyclisation reaction *via* attack of its alkoxide functionality at the *N*-Boc carbonyl to afford *O*-benzyl-oxazolidin-2-one **103** in 78% yield. The IR spectrum of **103** showed a characteristic new carbonyl stretch at 1754 cm^{-1} and **103** was sufficiently crystalline to allow X-ray structural analysis to be carried out (see Appendix). An α_D value comparable to that of the literature suggests that the integrity of the stereogenic centre of **103** had been conserved $[\alpha]_D$ -85.1 (*c* = 5.0, EtOAc), literature value [49] $[\alpha]_D^{rt}$ = -84.8).

(*S*)-4-(4-hydroxybenzyl)-oxazolidin-2-one **1** was then easily prepared in 92% yield by debenzylation of **103** using the catalytic hydrogenation conditions described by Burgess *et al.*[25] involving treatment with palladium on carbon in a mixed solvent system of methanol / ethyl acetate.

Finally, it should be noted that *all* of the intermediates in this synthetic protocol were *crystalline* enabling purification at each step of the synthesis to be achieved *via* simple recrystallisation of crude reaction products with no need for chromatography.

2.2.2 Synthesis of (S)-4-benzyloxazolidin-2-one (101).

(*S*)-4-benzyloxazolidin-2-one **101** is a classic Evans oxazolidin-2-one chiral auxiliary that was prepared according to the original method of Evans (see Scheme 2.2.2a).[44]



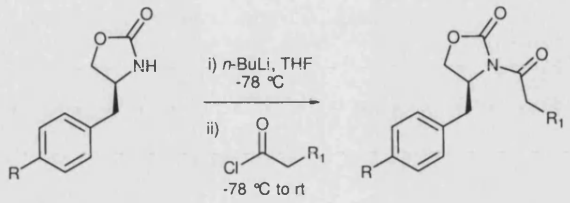
Scheme 2.2.2a: *Synthesis of (S)-4-benzyl-oxazolidin-2-one* **101** *according to the method of Gage and Evans.*[44]

Hence, L-phenylalanine was reduced to L-phenylalanol **108** in 71% yield *via* borane-mediated reduction of its acid functionality. The resulting amino alcohol was then treated with diethylcarbonate under basic conditions to form the oxazolidin-2-one **101** in 75% yield. An α_D value for **101** comparable to that of the literature demonstrated that the integrity of the stereogenic center had once again been conserved $[\alpha]_D^{rt}$ 5.1 (*c* 0.77, EtOH), literature value [44] $[\alpha]_D^{rt}$ 4.9 (*c* 1.10, EtOH).

2.3 Solution phase N-acylation studies

The first step of any oxazolidin-2-one mediated asymmetric reaction is attachment of the substrate to the oxazolidin-2-one *via* *N*-acylation. The conventional method of achieving *N*-acylation is *via* reaction of its lithium anion (generated with *n*-BuLi at -78 °C) with an acyl chloride (see Scheme 2.3a). This method was used successfully to acylate oxazolidin-

2-ones **101** and **103** with both *N*-propionyl and *N*-hydrocinnamoyl side-chains being attached in excellent 87-92% yields (see Table 2.3a).



101 R = H
103 R = OBn

Scheme 2.3a: *N-acylation of oxazolidin-2-ones* **101** *and* **103** *employing an acid chloride as the acyl source.*

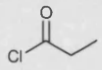
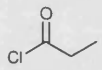
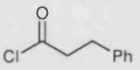
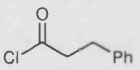
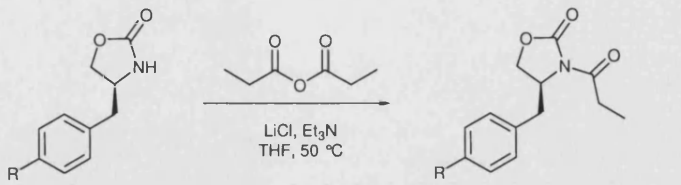
Entry	*Oxazolidin-2-one*	*Acid chloride*	*Product and (yield %)*
1	**101**		**109** (92) (R = H, R_1 = Me)
2	**103**		**110** (89) (R = OBn, R_1 = Me)
3	**101**		**111** (89) (R = H, R_1 = Bn)
4	**103**		**112** (87) (R = OBn, R_1 = Bn)

Table 2.3a: *N-acylation of oxazolidin-2-ones* **101** *and* **103** *employing an acid chloride as the acyl source.*

However, this *N*-acylation procedure does have some limitations, since it is not applicable to carboxylic acids that do not form stable acid halides, or substrates that are incompatible with the basicity of the lithiated oxazolidin-2-one. Although this was not the case for the *N*-propionyl side-chain, alternative, milder conditions were also investigated in case incompatible acyl substrates were encountered in the future.

One such method introduced by Ho and Mathre [50] employs a LiCl-activated anhydride as the acyl source, using triethylamine (Et_3N) as the base. Again, this reaction proceeded well with both oxazolidin-2-ones, affording **109** and **110** in essentially identical yields (83-89%) as the corresponding acid chloride variant (see Scheme 2.3b).



101 R = H
103 R = OBn

109 R = H (89 % yield)
110 R = OBn (83 % yield)

Scheme 2.3b: *N-acylation of oxazolidin-2-ones* **101** *and* **103** *employing an anhydride as the acyl source.*

2.4 Solution phase asymmetric enolate alkylation reactions

One of the most common applications of the Evans oxazolidin-2-one chiral auxiliaries is the asymmetric alkylation of chiral enolates of *N*-Acyl-oxazolidin-2-ones. In solution phase, chiral oxazolidin-2-one mediated asymmetric enolate alkylations have been found to proceed with excellent levels of diastereoselectivity.[51]

2.4.1 Mechanism of diastereocontrol

The success of chiral oxazolidin-2-ones in achieving such an efficient transfer of chirality is due to their ability to control crucial aspects of the asymmetric enolate alkylation reaction.

Selective enolisation is achieved due to 1,3-allylic strain between the oxazolidin-2-one ring and the substituent at the α-position where deprotonation occurs. In the case of enolisation of *N*-propionyl oxazolidin-2-one **113** with a non-nucleophilic base such as LDA or LHMDS at low temperatures (typically -78 °C) (see Fig 2.4.1a), conformer II is destabilised relative to conformer I due to 1,3-allylic strain between the methyl group at the α- position of the acyl chain and the bulky nitrogen substituents of the chiral auxiliary fragment. Hence an enolate is formed in which the methyl group and the nitrogen are positioned on opposite sides of the molecule thus affording the *cis*- or (*Z*)-enolate **113b**. It has been found for various *N*-Acyl-oxazolidin-2-ones that this process is generally highly selective, with > 98% (*Z*)-enolate being formed.[52]

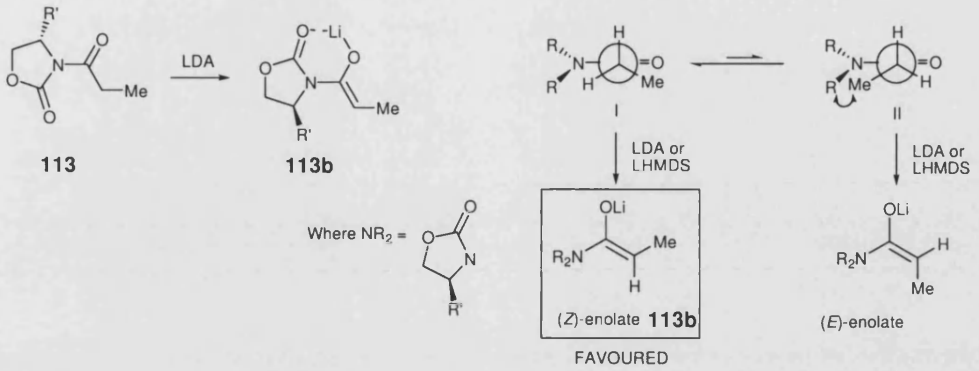


Fig. 2.4.1a: *Geometry of enolate formation controlled by 1,3-allylic strain between bulky nitrogen substituents of the oxazolidin-2-one ring and the α-substituent of the acyl side chain. Conformer I highly favoured due to minimisation of allylic strain and as a consequence get selective formation of the (Z)-enolate* **113b**.

With the geometry of the enolate defined, the R substituent of the oxazolidin-2-one auxiliary then provides a steric bias between the two faces of the enolate. Coordination of the lithium ion between the two carbonyl groups creates a planar, six-membered chelate ring that prevents rotation about the C-N bond. This fixes the bulky R group in a position such that the steric demand on the bottom face (as drawn in Fig. 2.4.1b) is large when compared to that of the top face. With inequivalent steric bias between the two faces of the enolate, the electrophile is more likely to attack the less-hindered top face and hence one diastereomer of the alkylated product is formed preferentially.

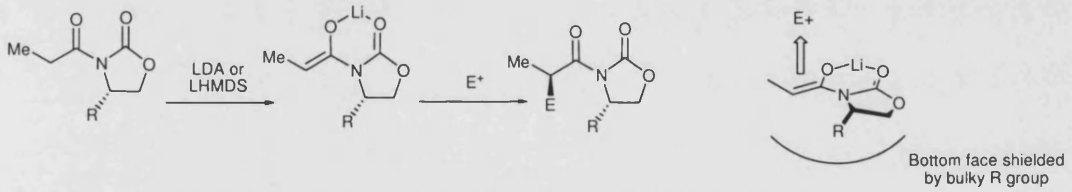
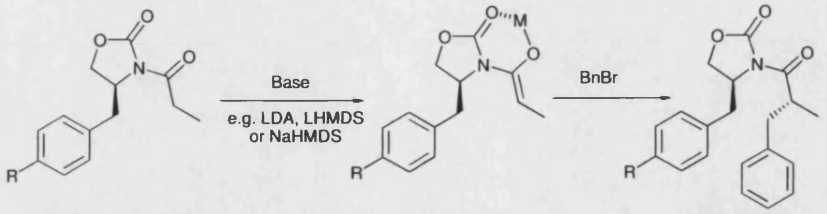


Fig. 2.4.1b: *Mechanism of diastereoselective control in enolate alkylation reaction.*

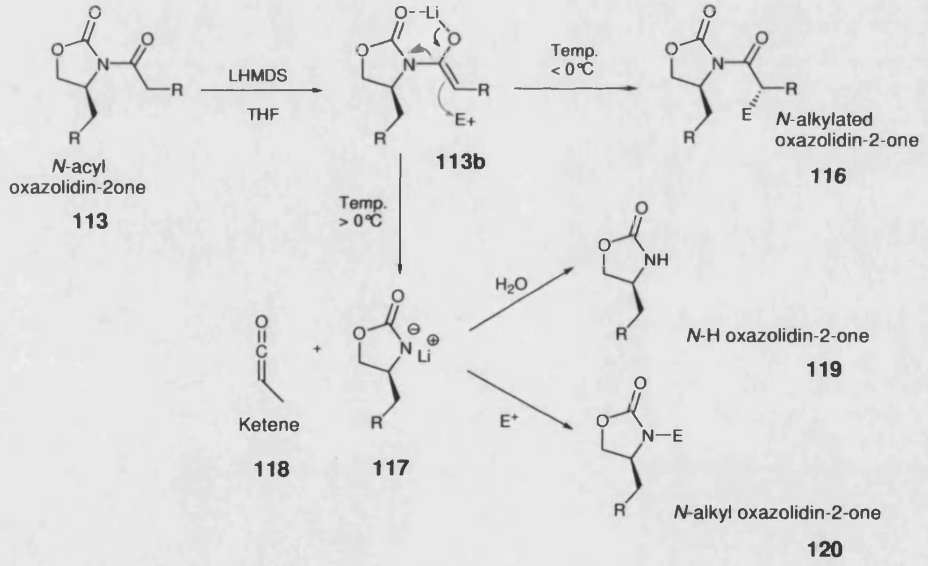
2.4.2. Solution phase asymmetric enolate alkylation reactions.

A typical reaction for the exploration of the potential of an Evans oxazolidin-2-one type chiral auxiliary is the asymmetric alkylation of the enolate of its *N*-propionyl derivative (see Scheme 2.4.2a).[53]



Scheme 2.4.2a: *Asymmetric enolate alkylation of N-propionyl oxazolidin-2-ones* **109** and **110** *with benzyl bromide.*

A review of the literature revealed that asymmetric enolate alkylation reactions of this type are prone to competing temperature-dependant enolate decomposition.[54] At temperatures above 0 °C, it has been reported that lithium enolates **113b** undergo extensive decomposition (see Scheme 2.4.2b, red arrow) to form *N*-lithiated oxazolidin-2-one of the form **117** and ketene **118**. The *N*-lithiated oxazolidin-2-one **117** is then quenched with any excess electrophile present in the reaction to form *N*-alkyl species **120**, or reacts with water on aqueous quenching of the reaction to form the parent *N*-H oxazolidin-2-one **119**.



Scheme 2.4.2b: *Temperature-dependant lithium enolate decomposition. The green arrow shows the desired reaction pathway to form N-alkylated oxazolidin-2-one* **116**, *wheresas the red arrow depicts the undesired side reaction involving decomposition of enolate* **113b** *to form N-lithiated oxazolidin-2-one* **117**.

Similar decomposition is reported to occur with the corresponding sodium enolate, which occurs at even lower temperatures, with temperatures of -78 °C being required for good yields of α-alkylated-*N*-acyl-oxazolidin-2-ones **116** to be achieved.

Therefore, for the case of the asymmetric alkylation of the enolate of *N*-propionyl oxazolidin-2-ones **109** and **110** with benzyl bromide, there were five possible products each that could be present at the end of the reaction, see Figure 2.4.2a.

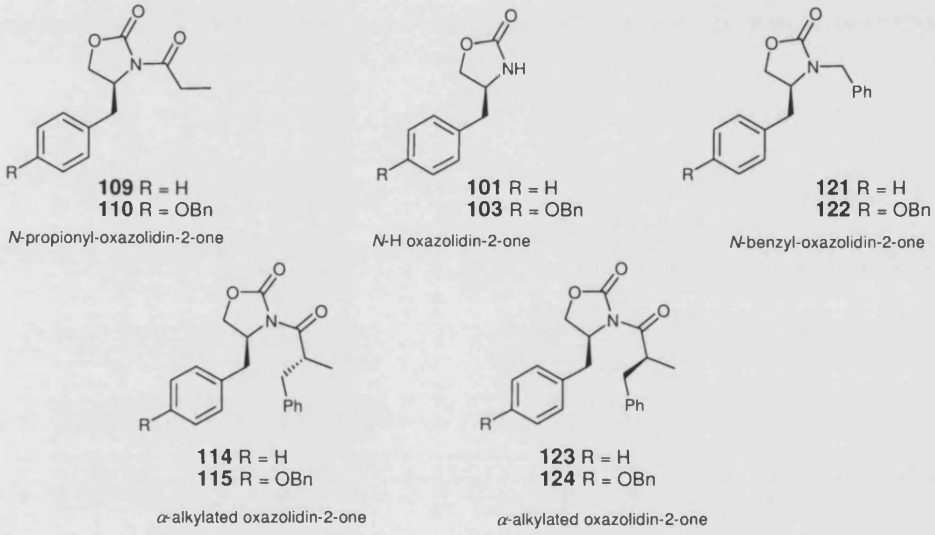
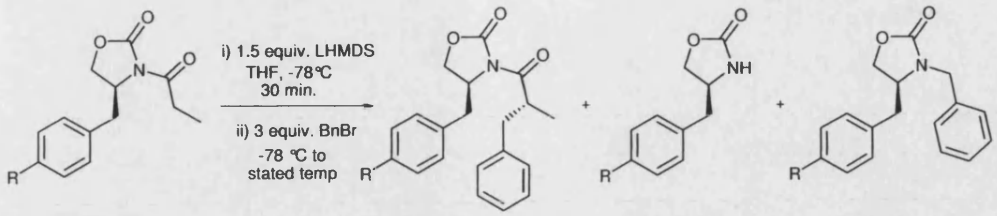


Fig 2.4.2a: *Potential products of enolate alkylation reaction of N-propionyl oxazolidin-2-one* **109** and **110** *with benzyl bromide.*

It was therefore decided to carry out a series of solution phase studies aimed at identifying any features of the asymmetric reactions in solution phase that might affect the performance of an analogous solid-supported system, where this competing enolate decomposition pathway had the potential to cause serious problems (see Chp. 3.1 for full discussion). Experiments were therefore conducted on solution phase oxazolidin-2-ones **101** and **103** to determine whether this decomposition pathway could be minimised or eliminated by careful control of reaction conditions.

Therefore, a series of reactions were conducted in which solutions of oxazolidin-2-ones **109** and **110** in THF were each treated with 1.5 equivalents of LHMDS at -78 °C for 30 minutes before addition of benzyl bromide. Each optimisation reaction was then stirred for a further

hour at -78 °C before being warmed slowly over 12 hours to a varied maximum temperature (see Scheme 2.4.2c).



109 R = H
110 R = OBn

114 R = H
115 R = OBn

101 R = H
103 R = OBn

121 R = H
122 R = OBn

Scheme 2.4.2c: *Enolate alkylation reaction of N-propionyl oxazolidin-2-ones* **109** and **110** *with benzyl bromide.*

Entry	Acylated Chiral Auxiliary	Max. temp °C [a]	Crude product composition (%) [b]				de of **114** or **115** (%)[c]	Isolated yield of **114** or **115** (%)[d]
			109 or **110** (*N*-propionyl)	**114** or **115** (α-benzylated)	**101** or **103** (*N*-H)	**121** or **122** (*N*-benzyl)		
1	**109**	rt	0	65	25	10	*	50
2	**110**	rt	0	57	28	15	*	46
3	**109**	0	0	87	8	5	≥ 95	81
4	**110**	0	0	85	9	6	≥ 95	73
5	109	-15	0	90	8	2	≥ 95	87
6	110	-15	0	93	5	2	≥ 95	89

***Table 2.4.2a**: Investigating the effect of temperature on the extent of enolate decomposition.*

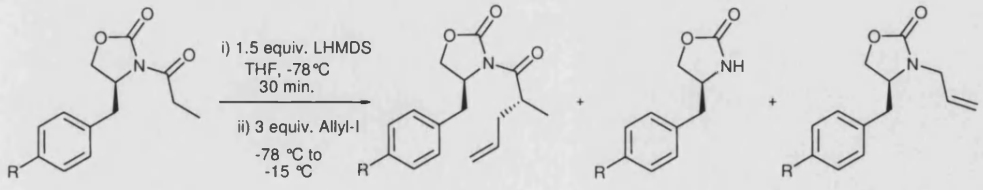
[a] LHMDS added to solution of oxazolidin-2-one **109** and **110** *in THF at -78 °C and stirred for 30 min, BnBr then added and reaction stirred at -78 °C for a further 1 hour then allowed to warm slowly to stated temperature over 12 hours. [b] Crude product composition determined by integration of the relevant signals in the 300 MHz ^{1}H-NMR spectrum. [c] All diastereomeric ratios determined by integration of the relevant signals in the 300 MHz ^{1}H-NMR spectrum corresponding to the benzylic protons of the major and minor diastereomers. Where stated as ≥ 95%, no trace of minor diastereomer was observed. * indicates de could not be reliably determined from analysis of the crude mixture or reaction products. [d] Isolated yield after recrystallisation.*

The results gained demonstrated that enolate decomposition is a significant problem in these reactions. As expected, when warmed to room temperature, there was extensive enolate decomposition which served to reduce the yields of alkylated product significantly

(see Table 2.4.2a, entries 1 and 2). With a maximum temperature of 0 °C, the extent of decomposition was greatly reduced (approx. 13-15% *N*-H-oxazolidin-2-one and *N*-benzyl-oxazolidin-2-one combined), resulting in improved yields of the desired alkylated product for both *N*-acyl-oxazolidin-2-ones **109** and **110** (see Table 2.4.2a, entries 3 and 4). This could be improved further by reducing the maximum permitted temperature to just -15 °C, where conversions of greater than 90% were observed for both oxazolidin-2-ones resulting in isolated yields of 87-89% of α-alkylated products **114** and **115** after recrystallisation (see Table 2.4.2a, entries 5 and 6). In all cases, the α-alkylated product was formed in high *de*, with no trace of the minor diastereomer being observed. It therefore appeared that maintaining the reaction temperature below -15 °C was sufficient to minimise the extent of enolate decomposition to an acceptable level without unduly compromising the reactivity of the system.

At this stage it was not deemed necessary to cleave the side-chain from the *N*-acyl-oxazolidin-2-one to determine the ee of the resulting chiral product, as a large number of non-racemising side-chain cleavage methods had been reported previously.[51,55,56] It was therefore assumed that the ee of any side-chain cleaved product would be identical to the *de* of the diastereomeric product before side-chain cleavage.

To assess the generality of these reaction conditions to other *N*-acyl-oxazolidin-2-ones and electrophiles, these conditions were used to react the enolates of both *N*-propionyl-oxazolidin-2-ones **109** and **110** with allyl iodide (see Table 2.4.2b, entries 1-2) and the enolates of both *N*-hydrocinnamoyl-oxazolidin-2-ones **111** and **112** with methyl iodide (see Table 2.4.2c, entries 1-2).



109 R = H
110 R = OBn

125 R = H
126 R = OBn

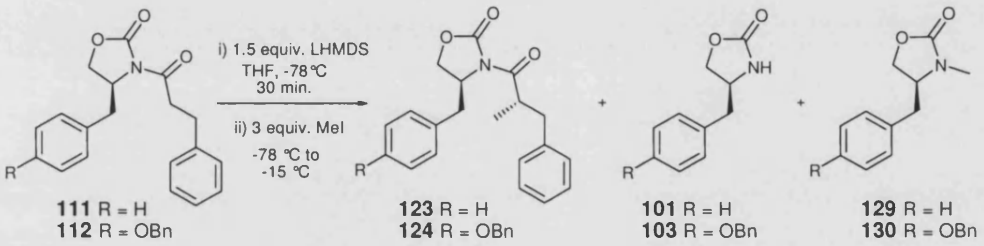
101 R = H
103 R = OBn

127 R = H
128 R = OBn

Scheme 2.4.2b: *Application of reaction conditions to N-propionyl-oxazolidin-2-ones* **109** *and* **110** *with allyl iodide.*

Entry	Acylated Chiral auxiliary	Crude product composition (%) [a]				de of **125** or **126** (%) [b]	Isolated yield of **125** or **126** (%) [c]
		109 or **110** (*N*-acyl)	**125** or **126** (α-alkylated)	**101** or **103** (*N*-H)	**127** or **128** (*N*-alkyl)		
1	**109**	0	89	8	3	≥ 95	88
2	**110**	0	90	6	4	≥ 95	89

***Table 2.4.2b**: Application of reaction conditions to N-propionyl-oxazolidin-2-ones* **109** *and* **110** *with allyl iodide. Reaction conditions: LHMDS added to a solution of* **109** *or* **110** *in THF at -78 °C and stirred for 30 min., allyl iodide then added, stirred at -78 °C for a further 1 hour then allowed to warm slowly to -15 °C over 12 hours. [a] Crude product composition determined by integration of the relevant signals in the 300 MHz ^{1}H-NMR spectrum. [b] All diastereomeric ratios determined by integration of the relevant signals in the 300 MHz ^{1}H-NMR spectrum corresponding to the benzylic protons of the major and minor diastereomers. Where stated as ≥ 95%, no trace of minor diastereomer was observed. [c] Isolated yield after recrystallisation or column chromatography.*



111 R = H
112 R = OBn

123 R = H
124 R = OBn

101 R = H
103 R = OBn

129 R = H
130 R = OBn

Scheme 2.4.2c: *Application of reaction conditions to N-hydrocinnamoyl-oxazolidin-2-ones* **111** *and* **112** *with methyl iodide.*

Entry	Acylated Chiral auxiliary	Crude product composition (%) [a]				de of **123** or **124** (%) [b]	Isolated yield of **123** or **124** (%) [c]
		111 or **112** (*N*-acyl)	**123** or **124** (α-alkylated)	**101** or **103** (*N*-H)	**129** or **130** (*N*-alkyl)		
1	**111**	0	86	8	6	91	83
2	**112**	0	84	11	5	93	82

***Table 2.4.2c**: Application of reaction conditions to N-hydrocinnamoyl-oxazolidin-2-ones* **111** *and* **112** *with methyl iodide. Reaction conditions: LHMDS added to a solution of* **109** *or* **110** *in THF at -78 °C and stirred for 30 min., allyl iodide then added, stirred at -78 °C for a further 1 hour then allowed to warm slowly to -15 °C over 12 hours. [a] Crude product composition determined by integration of the relevant signals in the 300 MHz ^{1}H-NMR spectrum. [b] All diastereomeric ratios determined by integration of the relevant signals in the 300 MHz ^{1}H-NMR spectrum corresponding to the benzylic protons of the major and minor diastereomers. Where stated as ≥ 95%, no trace of minor diastereomer was observed. [c] Isolated yield after recrystallisation or column chromatography.*

Although yields were slightly less than the analogous benzyl bromide reactions, good results were demonstrated for the alkylation of *N*-propionyl oxazolidin-2-ones **109** and **110** with allyl iodide (see Table 2.4.2b, entries 1 and 2) with α-allylated products **125** and **126**

being formed in excellent de (≥ 95%). Similarly, alkylation of the enolates of *N*-hydrocinnamoyl-oxazolidin-2-ones **111** and **112** with methyl iodide resulted in good yields of α-methylated products, albeit with their *de* slightly reduced to 91-93% (see Table 2.4.2c, entries 1 and 2). However, this reduced level of diastereoselectivity when methyl iodide is employed as the electrophile has been reported previously [54] and is likely to be attributed to the small steric demand of this electrophile.

Gibson *et al.* had suggested previously that judicious choice of appropriate work-up conditions for of these types of enolate alkylation reactions could significantly increase yields of α-alkylated products,[57] with the most efficient system being achieved using 0.16 M pH 7 phosphate buffer. However, in my hands, parallel trials comparing this buffer to standard saturated ammonium chloride solution revealed no significant difference in product yields.

To conclude, the solution phase studies carried out have established conditions for the solution phase asymmetric enolate alkylation of a small sample of *N*-acyl-oxazolidin-2-ones. It was found that conducting the alkylation reactions initially at -78 °C and then allowing them to warm slowly to -15 °C, minimised decomposition of the enolate and hence increased yields of α-alkylated products.

With the enolate decomposition pathway minimised, it was anticipated that the 'solution phase' conditions established for this type of asymmetric enolate alkylation reaction would be suitable for transferral to solid support. Formation of any side-products from competing enolate decomposition would complicate solid phase reactions, so it was hoped that careful control of temperature could be used to minimise this pathway. It was also possible that the *N*-acyl-oxazolidin-2-one enolates might even be stabilised by their immobilisation onto solid support, since this would result in monomeric enolates that might be less prone to decomposition.

2.5 *Solution phase asymmetric aldol reactions.*

The aldol condensation is a reaction of fundamental importance in synthesis since the resulting substitution pattern of the product is a common feature of many natural products. As a result, stereoselective aldol additions have been the subject of intense study, however the diastereoselective synthesis of just one of four possible diastereomeric aldol products (see Scheme 2.5a) is not a trivial undertaking.

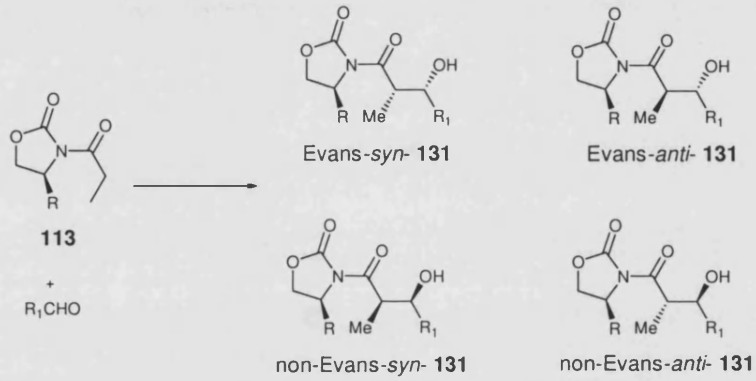
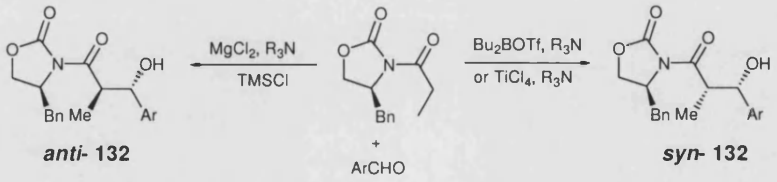


Fig. 2.5a: *Four possible diastereomeric products of the aldol reaction of N-propionyl-oxazolidin-2-one* **113** *with an aldehyde (R_1CHO).*

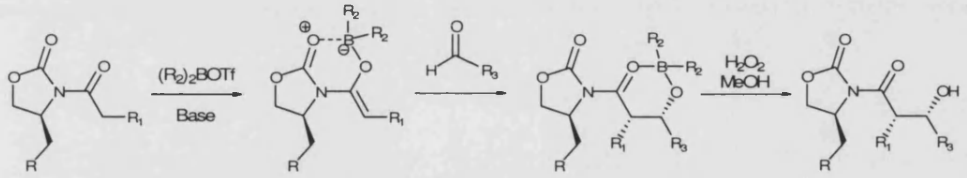
However, *N*-acyl-oxazolidin-2-one-mediated aldol reactions have proven to be highly diastereoselective and it is possible to select for different aldol diastereomers simply by changing the reaction conditions.[58] For example, aldol reactions of boron enolates of *N*-acyl oxazolidin-2-ones generally give 'Evans-syn'-aldol products ***syn*-132** in high de, yet reaction of the corresponding magnesium enolate gives the corresponding 'Evans anti'-diastereomer ***anti*-132** in high de [59] (see scheme 2.5b).



Scheme 2.5b: *The diastereoselectivity of aldol reactions of N-acyl-oxazolidin-2-ones is dependant on the reaction conditions.*

2.5.1 *Mechanism of diastereocontrol of syn-aldol reactions of boron enolates of N-acyl-oxazolidin-2-ones*

As for asymmetric enolate alkylation reactions, the success of an oxazolidin-2-one auxiliary in selectively preparing just one of four possible diastereomeric aldol products is due to its ability to firstly cause selective enolisation and secondly provide a stereofacial bias between the two faces of the enolate.



Scheme 2.5.1a: *General conditions for the aldol reaction of N-acyl-oxazolidin-2-one.*

Unlike enolate alkylation reactions where the lithium counter-ion acts as the Lewis acid for chelation of the transition state, Evans-*syn*-aldol reactions generally employ a di-substituted boron triflate as Lewis acid, with a separate non-nucleophilic base such as diisopropylethylamine (DIPEA) for enolisation (see Scheme 2.5.1a).

In order for the aldol reaction to proceed with high *syn*-diastereoselectivity, the enolate must first be formed with high levels of selectivity. Enolisation of *N*-acyl-oxazolidin-2-ones generally favours the (*Z*)-enolate due to allylic strain considerations (see Fig. 2.4.1a). The (*Z*)-geometry of the enolate then preferentially defines the relative stereochemistry of the two new stereocentres of the aldol product as *syn*- according to the Zimmerman Traxler model (detailed in Fig 2.5.1a).[52,60,61]

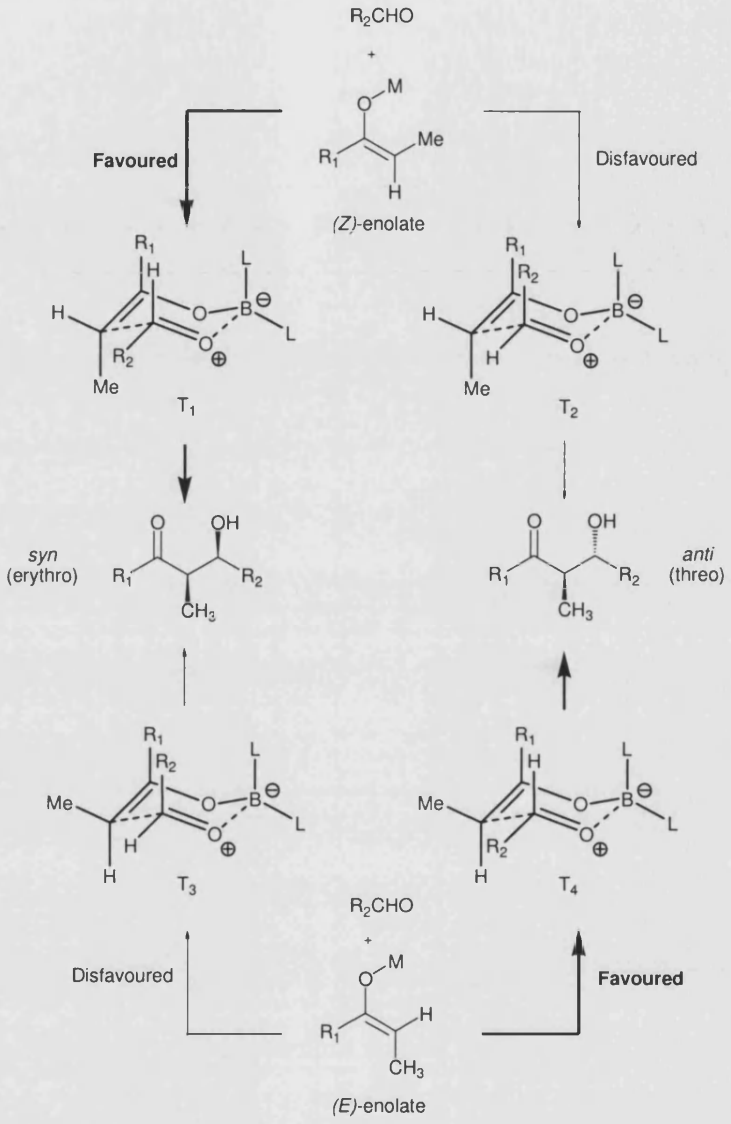
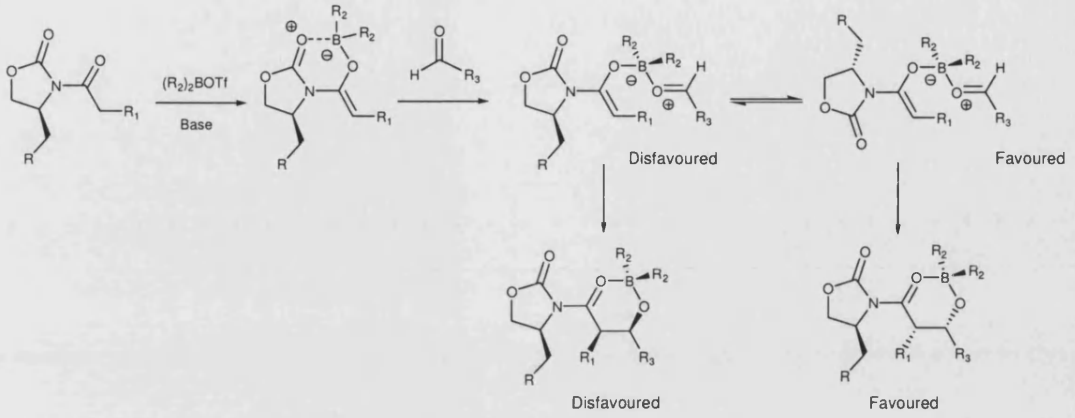


Fig 2.5.1a: *Zimmerman-Traxler transition states for translation of enolate geometry into stereochemistry in the aldol reaction.*

This Zimmerman-Traxler model postulates that the aldol reaction proceeds *via* a pericyclic 'chair-like' transition state. For *(Z)*-enolates, it is reasoned that T_2 is destabilised relative to T_1 due to unfavourable $R_1 \leftrightarrow R_2$ 1,3-diaxial interactions as well as $L \leftrightarrow R_2$ pseudo-1,3-diaxial interactions. Hence T_1 is the thermodynamically favoured transition state and the *syn* product is selectively formed. Likewise, for *(E)*-enolates, T_4 is favoured over T_3 and hence the *anti*-aldol product is formed preferentially.

Dialkylboron enolates (formed by enolisation with DIPEA in the presence of stoichiometric dialkylboron triflate) maximise $R_2 \leftrightarrow L$ steric interactions within the transition state due to relatively short boron-oxygen and boron-carbon (*i.e.* boron-ligand) bond lengths of 1.36-1.47 Å and 1.5-1.6 Å respectively, and this effect may be increased further by increasing the steric demand of the ligands co-ordinated to the boron centre. This results in the two transition states T_1 and T_2 having very different energies and hence results in a highly diasteroselective *syn*-aldol reaction. Furthermore, the use of a bulky dialkylboron reagent as Lewis acid ensures that $R_1 \leftrightarrow R_2$ interactions are small relative to the size of $R_2 \leftrightarrow L$ interactions, thus rendering the aldol reaction independent of the steric requirements of the enolate substituents R_1.

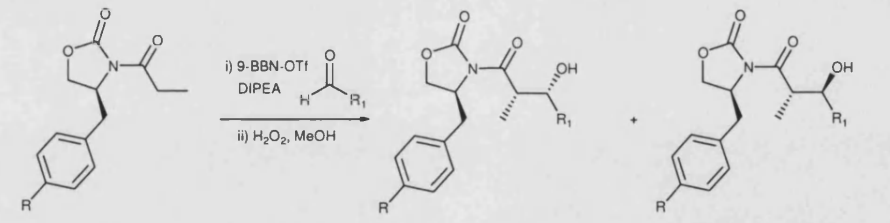
As discussed above, the enolate geometry determines the relative stereochemistry of the product so that potentially two *syn* diastereomers could be formed. However, in order to prepare just one diastereomer selectively, the absolute stereochemistry must be controlled by the chirality of the oxazolidin-2-one auxiliary introducing a steric bias between the two faces of the enolate. Upon addition of the aldehyde to a (*Z*)-dialkylboryl-enolate, the boron centre becomes associated with the aldehyde carbonyl group, rather than with the oxazoldin-2-one carbonyl. In the absence of chelation with the boron centre, the oxazolidin-2-one and its side-chain are not fixed in a rigid transition state. Rotation occurs around the carbon-nitrogen bond so that the oxazolidin-2-one carbonyl is *syn*-periplanar to the alkene functionality of the enolate. This results in the bulky R group of the oxazolidin-2-one projecting downwards (as drawn in Scheme 2.5.1b) and hence the aldehyde approaches preferentially from the opposite face to afford the observed *syn*-aldol diastereomer.



Scheme 2.5.1b: *Determination of absolute stereochemistry controlled by the bulky R group of the oxazolidin-2-one chiral auxiliary.*

2.5.2 Solution phase asymmetric syn-aldol reactions

A brief investigation into oxazolidin-2-one mediated *syn*-aldol reactions was then carried out in order to assess their suitability for transferral to solid support. Using reaction conditions optimised within the SDB research group,[62,63] *N*-propionyl-oxazolidin-2-ones **109** and **110** were enolised *via* treatment with 1.1 equivalents of 9-BBN-OTf and DIPEA, followed by addition of either isobutyraldehyde or benzaldehyde (see Scheme 2.5.2a) to form *syn*-aldol products in acceptable yield after column chromatography and in excellent *de*.



Scheme 2.5.2a: *Solution phase oxazolidin-2-one mediated syn-aldol reactions. 1.1 equiv. of 9-BBN-OTf added to N-propionyl oxazolidin-2-one* **109** or **110** *in DCM at 0 °C, and stirred for 10 minutes before 1.2 equiv. of DIPEA added. Reaction stirred for a further 30 min before cooling to -78 °C and addition of 1.3 equiv. of isobutyraldehyde or benzaldehyde. Reaction stirred at -78 °C for 1hr then allowed to warm to room temperature over two hours before quenching with pH7 phosphate buffer, methanol and H_2O_2 to cleave the boron-oxygen bond.*

Entry	Oxazolidin-2-one	Aldehyde	Product and yield (%)[a]	de (%)[b]
1	**109**		***syn*-133** (71) (R = H, R_1 = ^{i}Pr)	≥ 95
2	**110**		***syn*-134** (73) (R = OBn, R_1 = ^{i}Pr)	≥ 95
3	**109**		***syn*-135** (75) (R = H, R_1 = Ph)	90
4	**110**		***syn*-136** (69) (R = OBn, R_1 = Ph)	87

Table 2.5.2a: *Solution phase aldol reactions of N-propionyl-oxazolidin-2-ones* **109** and **110** *with isobutyraldehyde and benzaldehyde.* [a] *Isolated yield after column chromatography.* [b] *De determined by integration of the relevant signals in the 300 MHz* ^{1}*H-NMR spectrum corresponding to the CHOH protons of the syn and anti aldols. Where stated as* ≥ *95%, no trace of anti-diastereomer was observed.*

While the 69-75% yields of aldol products formed were acceptable, it was clear from analysis of the ^{1}H-NMR spectra of the crude reaction product that some unreacted starting material remained. The propensity of this class of aldol reaction to not proceed to completion has been noted previously within the SDB group and is generally thought to be related to the quality of the boron reagent employed in the reaction.

These findings indicated that this type of *syn*-aldol reaction was a suitable candidate for transferral to solid support, however a review of the literature revealed that the use of an excess of boron reagent could, in some cases, cause reversal of the stereochemistry of the aldol products formed.[33] The use of an excess of reagents is a commonly used technique in solid-phase chemistry to force reactions to completion, therefore this feature could potentially limit the reaction conditions available.

2.6 Conclusions

This chapter has described the first steps towards the development of an optimal solid-supported chiral auxiliary system for asymmetric synthesis. An Evans oxazolidin-2-one was selected to act as the chiral auxiliary due to its proven excellence in achieving consistently high levels of diastereoselectivity in a wide variety of solution phase reactions. To allow facile attachment to a variety of linkers, a phenol moiety was included as part of the stereocontrolling R group and a new, convenient synthetic strategy to oxazolidin-2-one fragment **1** was established.

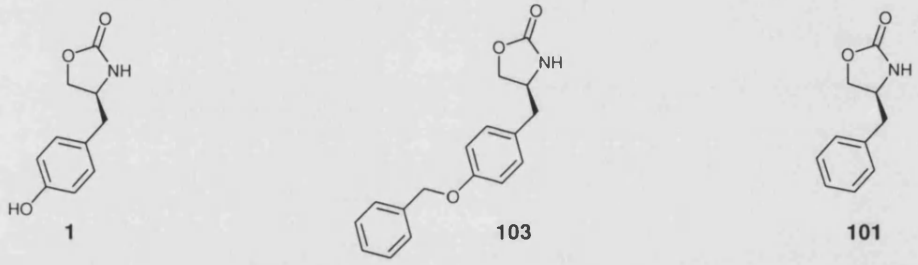


Fig 2.6a: *Preparation of oxazolidin-2-one auxiliaries* **1**, **103** *and* **101** *described in this chapter, with* **103** *and* **101** *employed in subsequent asymmetric reactions.*

In addition, two oxazolidin-2-one auxiliaries (**103** and **101**) suitable for solution phase optimisation studies were prepared and subsequently *N*-acylated with two different side chains. The resulting *N*-acyl-oxazolidin-2-ones were then subjected to asymmetric enolate alkylation and aldol reactions. In the case of enolate alkylation reactions, it was found that a temperature-dependant enolate decomposition pathway could occur to afford undesirable by-products, however these could be minimised by maintaining the reaction temperature below -15 °C. The α-alkylated products formed were produced in good yield and excellent *de*. For diastereoselective aldol reactions, *syn*-aldol products were formed in acceptable yield and with high levels of diastereoselectivity.

Importantly, there appeared to be no significant difference between the functioning of the conventional 4-benzyl-oxazolidin-2-one **101** and benzyloxybenzyl-oxazolidin-2-one **103**. **103** was intended to act as a solution phase mimic of the solid phase system with the *O*-

benzyl protecting group mimicking the polystyrene support, so its successful use as a chiral auxiliary represented a promising starting point for development of a solid-supported oxazolidin-2-one.

With multigram quantities of oxazolidin-2-one **1** available for immobilisation, the next step towards the development of a polymer-supported chiral auxiliary was the selection of the other components of the system. Therefore, my next goal was to identify a suitable polymer support and linker for immobilisation and establish a series of basic reactions on solid support.

Chapter 3: Developing a system for polymer-supported asymmetric synthesis.

Introduction

Chapter 2 discussed the selection of an Evans-type oxazolidin-2-one chiral auxiliary for use in our polymer-supported system, primarily due to its efficiency, versatility and popularity in solution phase asymmetric reactions. In addition, the synthesis of key oxazolidin-2-one fragments was described and the subsequent use of these oxazolidin-2-ones as chiral auxiliaries demonstrated in solution phase asymmetric enolate alkylation and aldol reactions. This chapter describes the crucial selection of the other components of the solid-supported chiral auxiliary system, namely the polymer support and the linker which plays a key role in attaching the chiral auxiliary to the polymer support. In addition, this chapter discusses the optimisation of some fundamental solid supported reactions essential to the development of a polymer-supported chiral auxiliary. These include immobilisation of the chiral auxiliary onto the chosen polymer support and the subsequent cleavage of various products both as the final stage of the synthetic process and for characterisation of key intermediates.

3.1 Selection of Resin

A solid supported chiral auxiliary requires three main components: a chiral auxiliary unit, a polymer support and a suitable linker to attach the two fragments together.

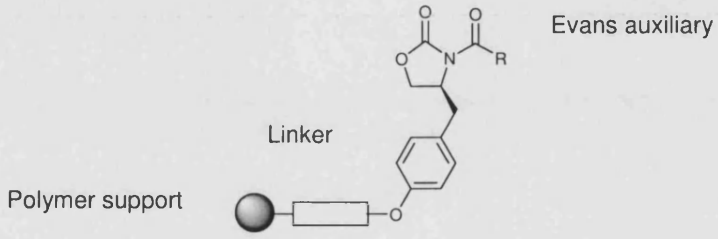


Fig 3.1a: *Essential components of a solid supported chiral auxiliary.*

The chiral auxiliary fragment must function efficiently and reliably for a range of asymmetric reactions and must also be tolerant of the presence of the solid support. The polymer support itself must be both mechanically and chemically stable whilst also inert to a range of reaction and cleavage conditions. If these conditions are not met then the polymer support will not be recyclable and will lose reactivity between each reaction cycle. The linker is a crucial component - it acts as a double-ended protecting group that attaches the chiral auxiliary to the solid support. Principally, the linker must be robust towards the reaction conditions, however it would be greatly advantageous if the linker could also be engineered to allow orthogonal cleavage of the chiral auxiliary fragment from the polymer support under mild conditions. This would allow polymer-supported reaction products and intermediates to be analysed easily in solution phase. The selection of each of the key components of this orthogonal cleavage strategy will now be discussed individually.

The decision to use a phenol-functionalised oxazolidin-2-one fragment derived from L-tyrosine, as a chiral auxiliary has been discussed in the previous chapter. To summarise, this fragment is relatively cheap and convenient to prepare in 4 steps from commercially available *N*-Boc-L-tyrosine (see Chapter 2) and there is precedent for its attachment to various polymer supports and its use for asymmetric synthesis.[25,30-32,35]

The polymer support plays a crucial role in solid supported reactions and picking the right support was likely to be fundamental to the success of this project. Although there are many different types of insoluble supports available, there are two main classes that dominate the literature. The first type is the traditional cross-linked polystyrene support that is widely used for polymer supported synthesis of peptides and small organic compounds. The second class, TentaGel™-type supports, are based on polystyrene cores grafted with polyethylene glycol (PEG) chains. The PEG chains dramatically affect the swelling properties of the resulting polymer support and can offer advantages for selected reaction scenarios.

Polystyrene resins (ps-resins), similar to those first developed by Merrifield in 1963 for peptide synthesis,[64] are the mainstay of solid supported chemistry. Advances in polymerisation techniques have resulted in the commercial availability of resins with predictable, reproducible and high loadings, and excellent mechanical and chemical stability profiles. They are readily and cheaply available from a multitude of commercial sources with a huge variety of pre-attached functional groups and different degrees of crosslinking available.[65] It is therefore becoming increasingly possible to cheaply purchase a polystyrene support of precise specifications to suit the requirements of a given project.[66] However, polystyrene supports are not without their limitations, notably the inherent hydrophobicity of the polystyrene core that can render them incompatible with polar solvents due to restricted swelling of the polymer bead limiting accessibility of reagents to the reaction sites located within the polymer.

PEG-grafted polystyrene resins (e.g TentaGel™) were designed to overcome this issue by attaching highly hydrophilic PEG chains to the resin, see Fig 3.1b.

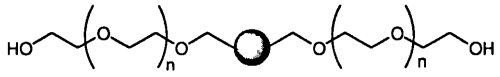


Fig 3.1b: *Schematic representation of PEG resin, a composite of cross-linked hydroxyethylpolystrene and 3000-4000 M.W. polyethylene glycol, which has been terminally functionalised.*

These side chains comprise approximately 75% of the resin mass, and afford resins that display excellent compatibility with polar solvents. However, the use of PEG-resins has its limitations, since uncontrolled swelling can afford polymers that are unsuitable for solid phase organic synthesis, resulting in resins that are 'sticky' and difficult to manipulate.[67] Furthermore, these resins also suffer from a lower loading of functional groups and are considerably more expensive than their polystyrene counterparts.

Considering the specific chemical requirements of our polymer-supported chiral auxiliary system, the nature of the chemistry to be performed dictates the use of relatively non-polar solvents (CH_2Cl_2 and THF) that will induce high levels of swelling in ps-resins. Also, much of the chemistry carried out using Evans' auxiliaries relies fundamentally on complexation of the oxazolidin-2-one to a Lewis acid. With TentaGel™-type resins the potential exists for the long PEG chains to also complex with Lewis acids, thus interfering with the mechanism of these types of asymmetric reactions.[67] Therefore, considering all these factors, a decision was made to employ a polystyrene resin as a polymer support for immobilisation of the chiral oxazolidin-2-one fragment.

Selection of the final component, the linker, was perhaps the most crucial factor in designing the system. There were a number of factors to be considered, however the issue of characterisation was uppermost in our minds. In the past one of the major pitfalls of solid phase synthesis has been the difficulty of monitoring the progress of solid phase reactions and characterising the nature of solid phase species. Consequently, much work has been focused towards developing methods to characterise polymer supported intermediates 'on-bead' and many useful methods have now been developed for this purpose.

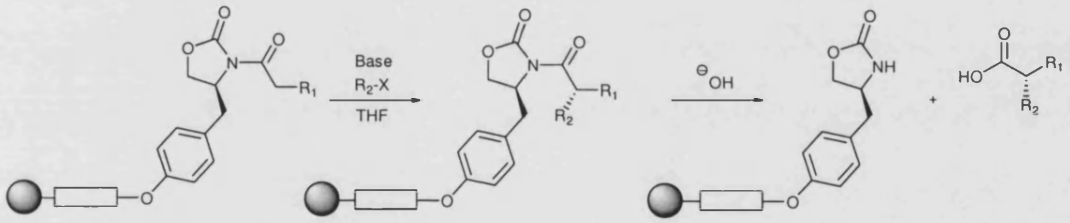
Magic angle spinning (MAS) NMR is now a well developed technique.[68] By rotating the sample of swollen polymer beads at the 'magic' angle of 54° to the direction of the magnetic field, the signals arising from the solid support are minimised and the line widths narrowed which allows reasonable spectra of the solid-supported species to be obtained (especially for ^{13}C-NMR). Also, specially designed high resolution probes have now been developed to further increase the speed and sensitivity of this technique. Another frequently used technique is single-bead FT-IR where a single resin bead is placed onto the

window of an IR microscope and analysed. However, both these techniques require specialised (and expensive) equipment which is not readily available to the wider chemical community and as a consequence these methods of analysis were not considered.

Alternative procedures for on-bead analysis include IR analysis of the resin beads crushed and suspended in KBr discs. This technique has been used in a quantitative manner using a polystyrene resin signal as an internal reference (e.g. the C=C-C peak at 1450 cm^{-1}) that is then compared with the intensity of a peak corresponding to an emerging or disappearing characteristic functional group.[69] However, this technique obviously suffers from the same limitations of IR in solution phase, as it can only give information on a few key functional groups with little information being available on the finer structure of a compound. Another possibility that was considered was the use of gel-phase NMR since Lorgé *et al.* have reported that slight modifications of the conditions used for acquisition in ^{13}C-NMR experiments can provide adequate spectra of well-swollen polystyrene beads without the need for specialised probes.[70] However, visualisation of quaternary carbonyls was difficult without the addition of a relaxation agent and analysis times were reasonably lengthy. The authors themselves claim the technique might not allow determination of the exact structure of a resin-bound species but would be a powerful complement to IR. It was therefore concluded that the non-destructive, on-bead analysis techniques readily available to us would not be sufficient to provide the detailed characterisation needed for optimisation of diastereoselective reactions 'on-bead'. A review of the literature revealed many other research groups had also reached this conclusion with by far the most widely used method for solid-phase reaction analysis being small-scale cleavage of polymer-supported intermediates and analysis by conventional solution phase methods.

It was therefore concluded that it would be considerably more convenient and efficient to incorporate an orthogonal cleavage strategy into our polymer-supported chiral auxiliary system. Thus, at any stage in a sequence of polymer supported reactions, cleavage of a portion of resin would allow solution phase characterisation of the auxiliary species, thus enabling unequivocal identification of any intermediates or side products produced 'on-bead'.

On consideration of such a strategy, it became apparent that it was highly unlikely that a single linker would be suitable for use in all the oxazolidin-2-one auxiliary-controlled asymmetric reactions that could be envisaged. Initially the focus of this study was to be the optimisation of solid phase asymmetric enolate alkylation reactions, therefore a solid phase system was targeted with this reaction in mind. In the course of an enolate alkylation reaction (see Scheme 3.1a), the linker would be exposed to a base (*e.g.* LDA, LHMDS or NaHMDS) and electrophiles (*e.g* benzyl bromide, allyl iodide), hence the linker would need to be stable to both classes of reagent. Additionally, in the subsequent nucleophilic side chain cleavage reaction (see Scheme 3.1a), the linker would need to be robust to nucleophilic (and basic) species such as hydroxide ions. Consideration of these chemical requirements resulted in selection of an acid-labile linker which would be robust under the reaction conditions, yet could be selectively cleaved under acidic conditions.



Scheme 3.1a: *Model transformation to be investigated: alkylation of the enolate of solid-supported N-acyl-oxazolidin-2-one with an electrophile, followed by nucleophilic side chain cleavage.*

A wide variety of acid-labile functionalised resins are commercially available that are capable of immobilising phenols.[71] These include chloromethyl polystyrene (Merrifield), *p*-benzyloxybenzyl alcohol (Wang), 2-chlorotrityl-chloride polystyrene and 4-(methoxyphenyl)-diisopropylsilyl propyl polystyrene. The extent of acid-lability, loading levels and cost of these resins varies considerably, as described in Table 3.1a.

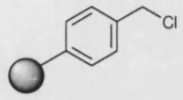
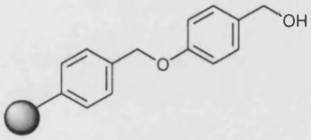
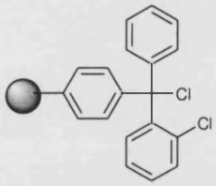
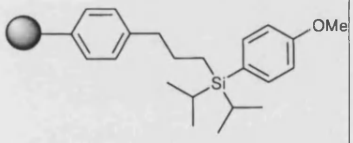
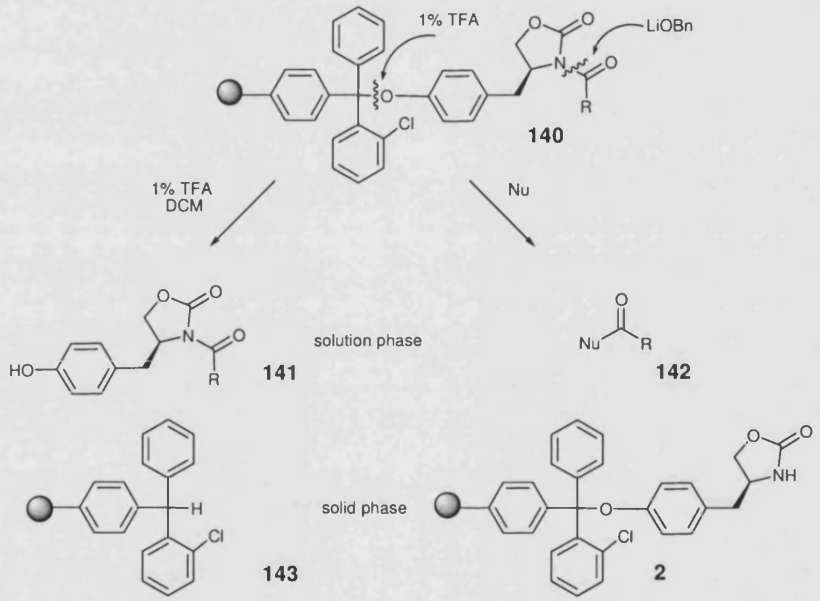
Structure and Name	Details [a]	Immobilisation conditions [b]	Acidic cleavage conditions [c]
 Merrifield	Loading 1.0 - 1.6 $mmolg^{-1}$ (£14 for 5 g)	NaH / KH + phenol, then 18-crown-6.	50-95% TFA or HF
 Wang	Loading 0.5 - 1.3 $mmolg^{-1}$ (£22 for 5 g)	Phenol + PPh_3 + DIAD.	15 – 50% TFA
 2-chlorotrityl chloride	Loading 0.8 -1.6 $mmolg^{-1}$ (£64 for 5 g)	Phenol + DIPEA / pyridine	1% TFA
 4-(methoxyphenyl)-diisopropylsilyl propyl polystyrene	Loading 1.2 -1.6 $mmolg^{-1}$ (£245 for 5 g)	Resin + TFMSA[d] (to prepare silyl triflate) then 2,6-lutidine + phenol.	5% HF in pyridine

Table 3.1a: *Possible acid-labile resins considered for use in this work, showing structure and details of loading, cost and conditions required for acid cleavage. All prices from NovaBioChem (Merck BioSciences).* [a] *All resins are 1% divinylbenzene-crosslinked and 100-200 mesh except 4-(methoxyphenyl)-diisopropylsilyl propyl polystyrene which is 50-100 mesh.* [b] *General conditions required to immobilise a phenol onto the solid support, according to NovaBiochem technical notes* [c] *General conditions required to cleave a phenol from the solid support, according to NovaBiochem technical notes.* [d] *TFMSA = Trifluoromethanesulfonic acid*

Although it is possible to cleave Merrifield resin, it is rarely demonstrated as the harsh conditions required often have adverse effects on both the polymer support and the attached substrate molecule. Wang resin (the preferred support of Burgess)[25] was also considered, although once again relatively harsh acidic cleavage conditions were likely to limit the range of compatible substrates. 4-(methoxyphenyl)-diisopropylsilyl propyl polystyrene, has desirable cleavage properties, however it requires pre-activation before use involving treatment with TFMSA to produce a polymer-bound silyl triflate, whilst it is also

prohibitively expensive. From consideration of these issues, 2-chlorotrityl chloride resin (1% DVB) (100-200 mesh) was selected as the polymer support of choice for our immobilisation studies since its mild acidic cleavage conditions would allow its use for the analysis of a wide variety of functionalised side-chain products.

The orthogonal cleavage system that would be produced by the use of 2-chlorotrityl chloride resin to immobilise the oxazolidin-2-one is described in Scheme 3.1b.



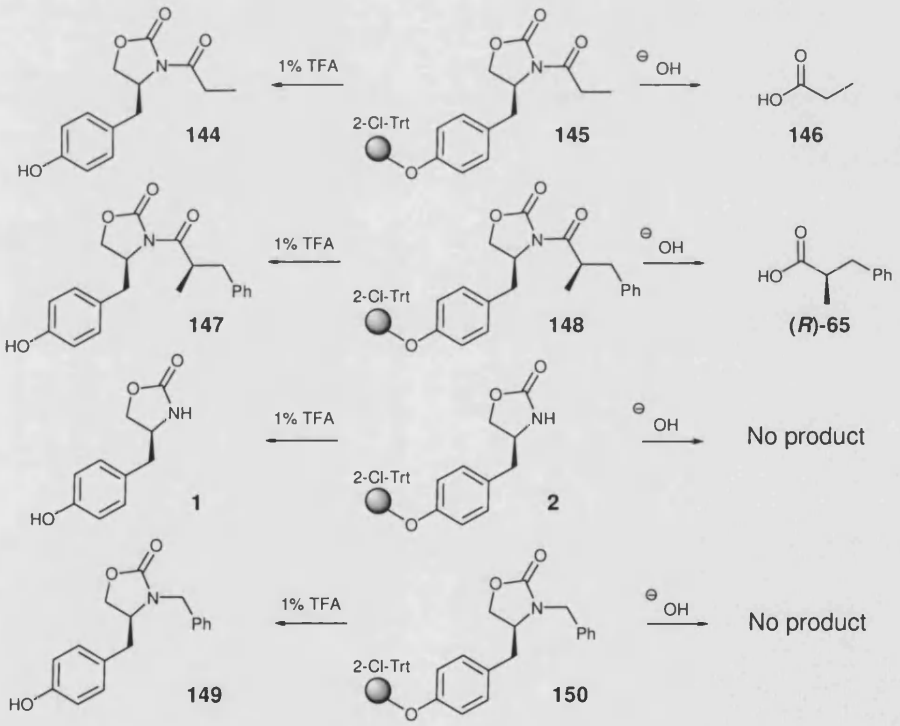
Scheme 3.1b: *Two possible orthogonal cleavage routes for functionalised resin* **140**, *showing both solution and solid phase products.*

Cleavage of reaction products from the resin could therefore be effected chemoselectively at two different locations to afford either the acyl side-chain fragment **142**, or the intact *N*-acyl oxazolidin-2-one fragment **141**.

Conventional nucleophilic side chain cleavage would release the side chain product **142** whilst leaving the chiral auxiliary fragment still attached to polymer support. This method of cleavage would therefore be used in an optimised system for the preparation of libraries of chiral side-chain products. The resin-bound auxiliary **2** would then be re-acylated and reused as required. Alternatively, for the purposes of method development, treatment with

TFA could be employed as an alternative cleavage strategy to release the entire *N*-acyl oxazolidin-2-one fragment **141** from polymer support. This would then enable polymer supported products to be readily characterised by comparison with authentic standards prepared previously *via* established solution phase methodology (see Chapter 2).

The utility of the two-point cleavage strategy can be illustrated by considering the potential products arising from alkylation of the enolate of *N*-propionyl oxazolidin-2-one **145** with benzyl bromide. Earlier solution-phase studies (see Chapter 2) had shown that a competing enolate decomposition pathway could account for the competing formation of parent *N*-H oxazolidin-2-one **2** and *N*-benzyl oxazolidin-2-one **149** (see Scheme 3.1c). It was therefore reasonable to assume that the corresponding solid-supported species would also be formed in these types of enolate alkylation reactions.



Scheme 3.1c: *Possible products of solid-phase alkylation reactions and their cleavage products.*

Conventional nucleophilic side chain cleavage of the acyl fragment from polymer support using LiOH would only reveal the presence of propionic acid **146** and α-methyl

hydrocinnamic acid (*R*)-**65** with no products derived from *N*-Benzyl oxazolidin-2-one **150** or parent *N*-H oxazolidin-2-one **2** being cleaved. However, cleavage of the resin using 1% TFA solution would result in four species, *N*-propionyl oxazolidin-2-one **144**, α-benzylated-oxazolidin-2-one **147**, *N*-H oxazolidin-2-one **1** and *N*-Benzyl oxazolidin-2-one **149**. Therefore this dual cleavage strategy would enable a true picture of what was occurring on polymer support to be ascertained, which would prove invaluable for reaction optimisation.

The ability to cleave the newly formed chiral products as diastereomers containing the chiral auxiliary fragment would also offer an advantage to reaction scenarios where poor levels of diastereoselectivity were achieved. If cleavage of a small portion of resin revealed that a poor de had been achieved, it would be considerably easier to enrich a diastereomeric product (*via* chromatography, recrystallisation etc.), than it would be to enrich a corresponding enantiomeric product resulting from nucleophilic side chain cleavage. Subsequent nucleophilic cleavage of the enriched diastereomer could then be employed to afford the enriched enantiomeric product. Although this scenario is by no means an efficient or desired solution, it does represent another potential advantage of the use of a 2-chlorotrityl-bound chiral auxiliary during the asymmetric reaction condition optimisation process.

Whilst 2-chlorotrityl chloride resin represents an incredibly useful development resin, it is reasonably expensive when compared to alternative ps-resins. The ultimate aim of this study was to develop an efficient, cheap and user-friendly system for the synthesis of libraries of enantiopure carboxylic acid derivatives. Consequently it was our intention to transfer this methodology to robust Merrifield resin once it had been optimised on the 2-chlorotrityl chloride development resin (see Chapter 5.3).

3.2. Immobilisation of auxiliary onto 2-chlorotrityl chloride resin

Initial attempts to immobilise the auxiliary fragment onto 2-chlorotrityl chloride resin employed *N*-propionyl oxazolidin-2-one **144** rather than *N*-H oxazolidin-2-one **1**. Although

it should be possible to attach *N*-H-oxazolidin-2-one **1** selectively *via* its phenol moiety (pK_a approx. 10) rather than the carbamate NH (pK_a approx. 12) *via* judicious choice of base, it was decided to eliminate this potential complication at this stage.

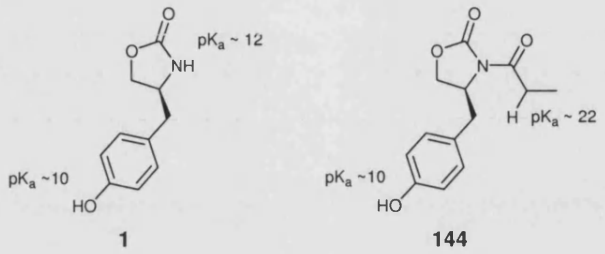
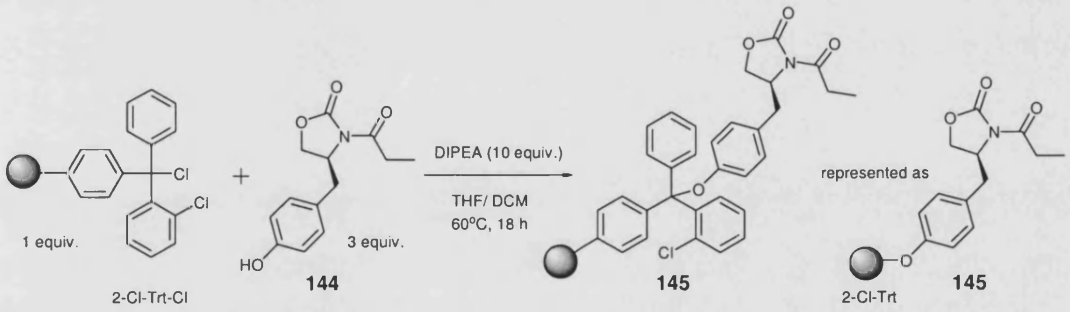


Fig 3.2a: *Estimated pK_a values of functional groups of oxazolidin-2-one auxiliary fragments* **1** *and* **144**. [72]

Early literature examples describing the immobilisation of functionalised phenols onto 2-chlorotrityl chloride resin involved heating the resin and a functionalised phenol at 50 °C for 18 h in the presence of a large excess of pyridine.[73] However,this route was found to be highly unreliable, with later reports claiming that these conditions resulted in pyridine reacting with the chlorotrityl group.[74] Alternative conditions employed the more hindered base diisopropylethylamine (DIPEA) at 25 °C in a mixed DCM/THF solvent.[75-77] Hence phenolic auxiliary fragment **144** (3 equiv.) was stirred with 2-chlorotrityl-chloride resin (1 equiv.) with DIPEA (10 equiv.) in a mixture of DCM and THF for 24 h. This method was found to immobilise the phenolic auxiliary fragment in a reliable and reproducible manner with highest yields achieved when heating the reaction at 60 °C for 18 h.



Scheme 3.2a: *Immobilisation of N-propionyl auxiliary* **144** *onto 2-chlorotrityl chloride resin.*

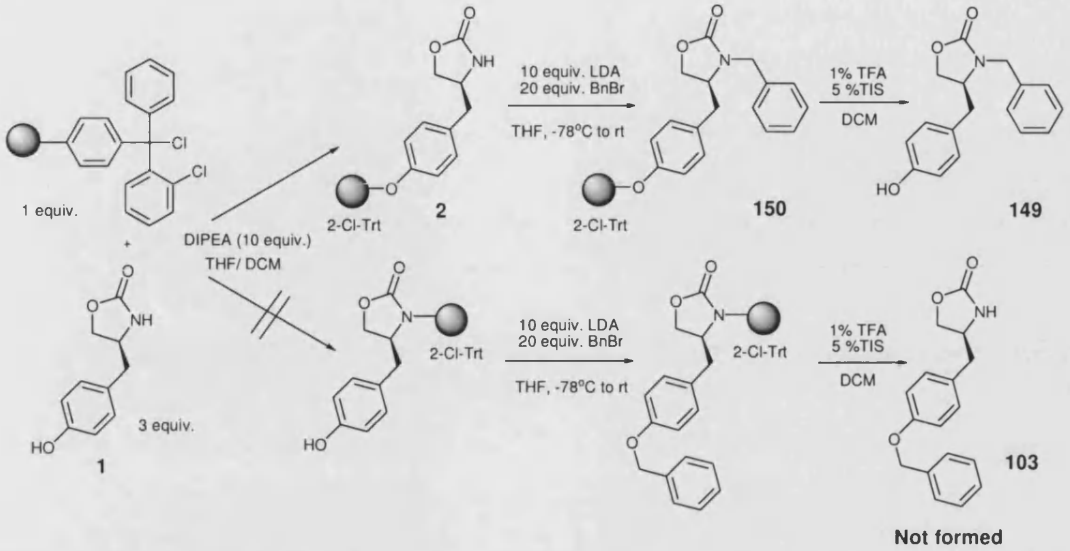
The excess auxiliary fragment was easily recovered at the end of the immobilisation reaction by sequential washing of the resin with DCM, DCM / MeOH and MeOH, and evaporation of solvent *in vacuo* to afford impure *N*-propionyl oxazolidin-2-one **144** that

was then redissolved in ethyl acetate followed by a simple acid wash to remove residual DIPEA.

In this way two batches of resin **145** were prepared with loadings of 1.11 $mmolg^{-1}$ and 0.99 $mmolg^{-1}$ (as estimated by mass of recovered material after TFA cleavage (*vide infra*)). IR analysis (KBr disc) of the resin revealed two characteristic carbonyl peaks at 1780 cm^{-1} and 1700 cm^{-1}. The stereochemical integrity of the auxiliary was not compromised during the immobilisation reaction as shown by measurement of the α_D values of the chiral *N*-propionyl oxazolidin-2-one **144** recovered from reaction washings and from TFA cleavage of the functionalised resin.*

The preparation of a versatile *N*-H auxiliary-functionalised resin that could later be acylated with the side-chain of choice was next investigated as this would represent a more efficient (and potentially commercially viable) route to a variety of different *N*-acyl-oxazolidin-2-one resins. Examination of the pK_a values of DIPEA ($pK_a \approx 14$) and the two functional groups of auxiliary **1** (phenol $pK_a \approx 10$, carbamate $pK_a \approx 12$) suggested that the polymer derivatisation method described above could also be employed to selectively immobilise unprotected **1** onto 2-chlorotrityl-chloride resin through its phenolic group. This was confirmed by solid phase studies whereby 2-chlorotrityl chloride resin was first functionalised by treatment with 10 equiv. DIPEA and 3 equiv. oxazolidin-2-one **1** to afford a polymer that was then treated with 10 equiv. LDA and 20 equiv. BnBr. Cleavage of this 'benzylated' polymer with 1% TFA in DCM resulted in exclusive formation of *N*-benzyl-oxazolidin-2-one **149**, with no evidence of any *O*-benzyl-oxazolidin-2-one **103** having been formed. Therefore this cleavage experiment clearly revealed that oxazolidin-2-one **1** had been exclusively immobilised onto polymer support *via* its phenolic group.

* **144** before any treatment: α_D 42.5° (*c* 0.4, $CHCl_3$), **144** recovered from reaction washings: α_D 41.9° (*c* 0.5, $CHCl_3$), **144** recovered after TFA cleavage of functionalised resin: α_D 43.2° (*c* 0.4, $CHCl_3$).



Scheme 3.2b: *Solid phase studies into selectivity of immobilisation of NH, OH auxiliary* **1**, *showing selective immobilisation via phenol group. For details of TFA cleavage reaction to remove entire auxiliary fragment from resin see Section 3.4.1. (TIS = Triisopropylsilane).*

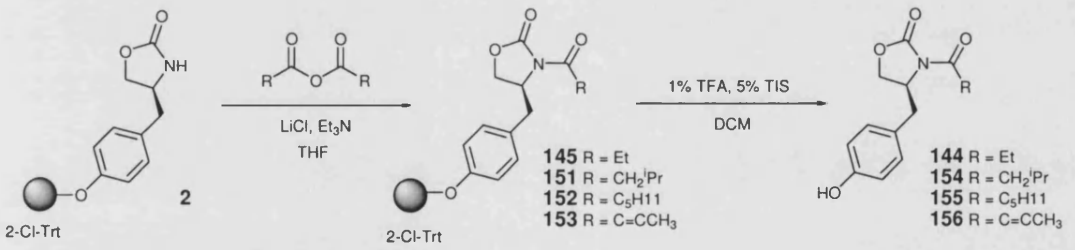
Optimisation of the previous immobilisation method was then carried out due to the increased polarity of the parent oxazolidin-2-one fragment **1** relative to its *N*-propionyl analogue **144**. It was found necessary to aid the solvation of **1** during the immobilisation reaction by the addition of a small amount of DMF (typically 2 mL per g of resin). The procedure for recovery of the excess auxiliary fragment was also altered slightly due to the increased water solubility of **1** that lead to poor yields when an acidic aqueous work-up was employed. Therefore, the filtrate recovered from the washing of the resin was evaporated to dryness, then redissolved in MeOH and purified by passing through a solid phase extraction column (SCX-2). This column, packed with supported propylsulfonic acid residues, scavenged the excess basic DIPEA allowing the non-basic oxazolidin-2-one **1** to be eluted in an essentially pure form.

Again, the batches of chiral oxazolidin-2-one resin **2** produced were of good yield, typically between 0.96-1.16 $mmolg^{-1}$, 80– 96% yield, based on mass recovery of **1** after TFA cleavage, (*vide infra*). Measurement of α_D values confirmed that the configuration of the stereocentre of auxiliary **1** had been conserved throughout the immobilisation/cleavage

process.* Importantly, IR analysis (KBr disc) of the resin showed a characteristic broad peak at 1752 cm^{-1} corresponding to the oxazolidin-2-one carbonyl.

3.3 N-Acylation of the oxazolidin-2-one fragment 'on-bead'

A review of the literature revealed that the most common method for *N*-acylating a solid-supported oxazolidin-2-one auxiliary is *via* the use of an anhydride acyl donor. In previous solution phase work (*vide supra*), conditions employing the use of anhydride, lithium chloride and triethylamine in THF (based on the method of Burgess) [25] had been found to afford *N*-acyl oxazolidin-2-ones in excellent yield. Consequently, these conditions (five equivalents of each reagent) could be used to drive the *N*-acylation reaction to completion, producing a range of *N*-acyl oxazolidin-2-ones in essentially quantitative yield. Therefore this anhydride approach was employed to prepare a variety of polymer-supported *N*-Acyl-oxazolidin-2-ones, including *N*-propionyl-**145**, *N*-isovaleryl-**151**, *N*-hexanoyl-**152** and *N*-crotonyl-oxazolidin-2-one-**153** in good yields.



Scheme 3.3a: *N-acylation of N-H oxazolidin-2-one functionalised resin* **2** *employing the appropriate anhydride, triethylamine and lithium chloride. Loading established by mass recovery of the product of cleavage of the entire oxazolidin-2-one fragment from the resin with 1% TFA (see Section 3.4.1).*

* **1** before any treatment: α_D -12.3° (*c* 0.65, MeOH), **1** recovered from reaction washings: α_D -12.0° (*c* 0.6, MeOH), **1** recovered after TFA cleavage of functionalised resin: α_D -11.9° (*c* 0.6 MeOH).

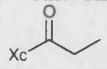
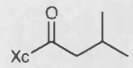
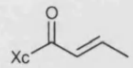
Side chain	Resin	Solution phase fragment [a]	Yield [b] (%)	Loading of *N*-Acyl oxazolidin-2-one resin
	**145**	**144**	88 – 96 [b]	1.01 – 1.15 $mmolg^{-1}$ [c]
	**151**	**154**	91	1.10 $mmolg^{-1}$
	**152**	**155**	75	0.91 $mmolg^{-1}$
	**153**	**156**	85	1.05 $mmolg^{-1}$

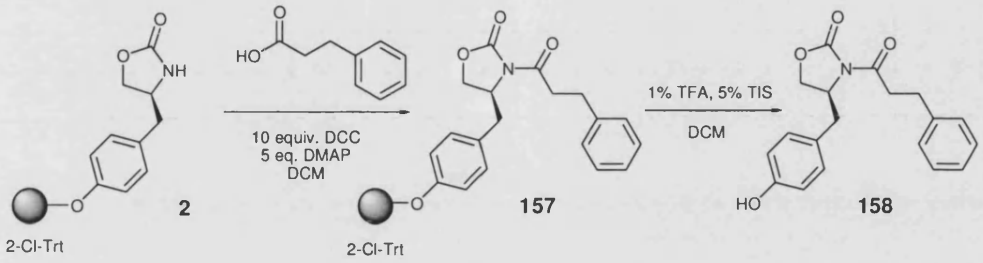
Table 3.3a: *Preparation of N-Acyl oxazolidin-2-one functionalised resins (2-chlorotrityl chloride resin) via N-acylation with the corresponding anhydride. X_c indicates a polymer-bound oxazolidin-2-one.* [a] *Solution phase N-acyl- oxazolidin-2-one prepared by TFA cleavage of N-acyl-oxazolidin-2-one resin.* [b] *Yield calculated by mass recovery of solution phase oxazolidin-2-one after TFA cleavage of 20 mg resin, based on original loading of resin (1.2 $mmolg^{-1}$).* [c] *Multiple batches of functionalised resin prepared.*

However, the general applicability of this *N*-Acylation method is restricted due to the limited availability of anhydrides. Although this issue could potentially be circumvented by *in-situ* formation of a mixed anhydride,[78] it was concluded that it would be more efficient to develop a method that would allow 'on-bead' acylation directly from the appropriate carboxylic acid.

There were two reported cases of achieving *N*-acylation *via* deprotonation of the polymer supported oxazolidin-2-one with *n*-BuLi or LHMDS followed by treatment with the acid chloride.[31,32] However, repeating these conditions resulted in only partial success in my hands. Polymer supported *N*-H oxazolidin-2-one **2** was treated with LHMDS (2 equivalents) at -20 °C for 2 hours before addition of hydrocinnamoyl chloride. The reaction was stirred at -20 °C for a further 2 hours then warmed slowly to room temperature for 12 hours. TFA cleavage of the resulting resin revealed some *N*-acylation had occurred, but the resultant ^{1}H-NMR spectra were swamped by unidentifiable impurities, some of which were clearly derived from an oxazolidin-2-one fragment.

As an alternative method of achieving *N*-acylation directly from the carboxylic acid, conditions were employed using the peptide coupling reagent DCC and catalytic DMAP in DCM in a variation of a solution phase literature procedure.[79] Again, an excess of reagents

was used since the solid phase nature of the reaction allowed facile removal of the urea by-product by repeated washing of the resin with DMF. Hence *N*-hydrocinnamoyl oxazolidin-2-one resin **157** was prepared in good yield.



Scheme 3.3b: *N-Acylation of solid-supported N-H oxazolidin-2-one* **2** *with hydrocinnamic acid mediated by DCC and DMAP.*

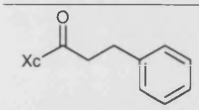
Side chain	Resin	Yield [a] (%)	Loading of *N*-Acyl oxazolidin-2-one resin
	**157**	80	0.96 $mmolg^{-1}$

Table 3.3b: *Acylation of solid-supported N-H oxazolidin-2-one with hydrocinnamic acid mediated by DCC and DMAP. In this case, X_c indicates polymer-bound oxazolidin-2-one.* [a] *Yield calculated by mass recovery of auxiliary fragment after TFA cleavage of 20 mg resin, based on original loading of resin (1.2 $mmolg^{-1}$).*

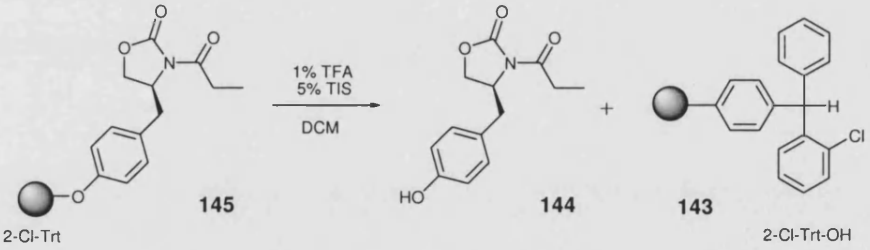
To summarise, in my experience, the most reliable, mildest and high yielding method for achieving *N*-acylation of our polymer supported *N*-H-oxazolidin-2-one **2** was by use of an anhydride approach. However, in those cases where the anhydride is not readily available, the DCC / DMAP route represents a viable alternative.

3.4 Cleavage from resin

Preliminary experiments were then undertaken on *N*-propionyl and *N*-isovaleryl functionalised resins **145** and **151** respectively to confirm that the proposed orthogonal cleavage methods were both viable and high-yielding.

3.4.1 TFA cleavage of the entire N-acyl-oxazolidin-2-one fragment from polymer support.

The extremely acid labile trityl linkage was easily cleaved by treatment with 1% TFA in DCM at room temperature (30 min.). The addition of triisopropylsilane (TIS) (5%) is reported to enhance the rate of the cleavage reaction due to its stabilising effect on the resulting trityl cation.[77] After treatment the resin was washed thoroughly with DCM and MeOH, with all washings collected and evaporated *in vacuo* to remove all residual traces of TFA. To confirm that initial treatment with TFA was sufficient to effect complete cleavage, the above process was repeated on the same sample of resin, but upon filtration and evaporation of this second cleavage reaction, no additional material was recovered, implying complete cleavage in the first round of treatment. IR analysis (KBr disc) of the TFA-treated resin also revealed a complete absence of carbonyl peaks, again suggesting complete release of the auxiliary from polymer support.



Scheme 3.4.1: *TFA cleavage to remove entire oxazolidin-2-one fragment from the 2-chlorotrityl-chloride resin.*

The mass recovery of non-volatile *N*-acyl-oxazolidin-2-one **144** from this TFA cleavage reaction was used to calculate the loading of the resin **145**. This procedure represents a reliable and relatively quick characterisation method using readily available equipment with accurate analysis being achieved from cleavage of just 20 mg of functionalised resin.

3.4.2 Nucleophilic side chain cleavage

The traditional method of removing the derivatised, chiral side chain product from the auxiliary is *via* nucleophilic cleavage. In solution phase syntheses, after the cleavage reaction, the side chain product is separated from the auxiliary by a variety of different methods including chromatography, distillation or acid/base extraction. In the case of a solid-supported system, the side-chain product would be released into solution with the auxiliary remaining immobilised. Product retrieval should then be achieved *via* simple filtration of the residual polymer and removal of the solvent *in vacuo*. By judicious choice of an appropriate nucleophile, this cleavage step could serve to introduce an extra point of diversity, thus enabling the preparation of a number of different derivatives such as carboxylic acids, esters, thioesters, amides, Weinreb amides and alcohols. However, the choice of nucleophile is not limitless as there are two important factors that must be considered. Firstly, the nucleophile must not cause racemisation of the newly formed chiral centre. Secondly, the nucleophile must attack the exocyclic carbonyl selectively and leave the endocyclic carbonyl of the polymer supported oxazolidin-2-one intact. The elimination of the endocyclic cleavage pathway is crucial both for the retention of high yields of side chain product and also to enable recycling and reuse of the polymer supported auxiliary.

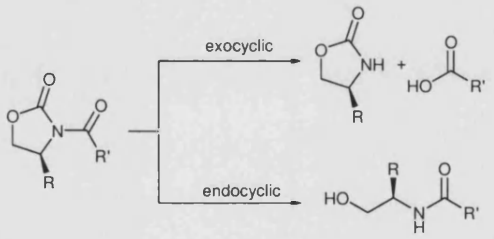


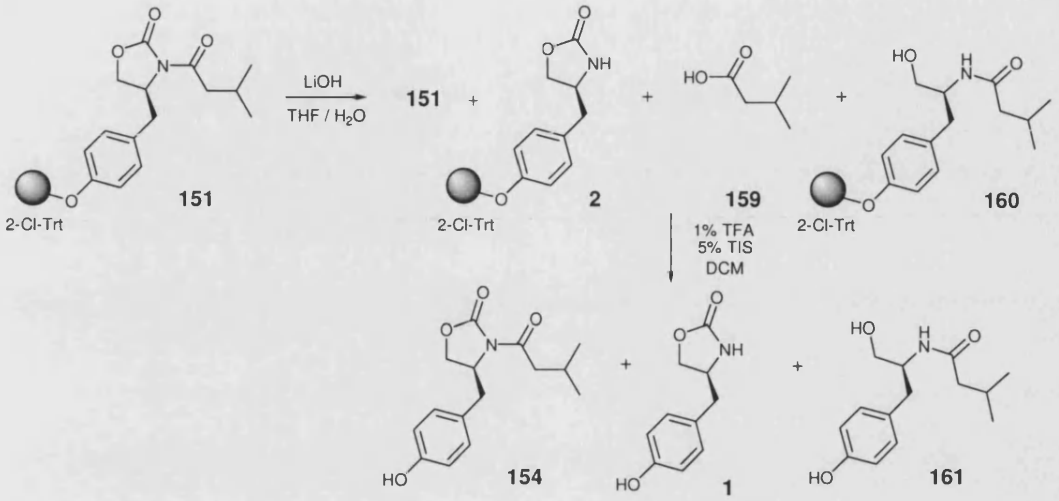
Fig 3.4.2: *Two competing pathways for nucleophilic cleavage of N-acyl-oxazolidin-2-one.*

In the absence of significant steric crowding around the exocyclic carbonyl, electronic factors generally direct nucleophilic attack in the desired exocyclic fashion. However, as the steric requirements of the R' group are increased, there is increased competition from the less sterically hindered endocyclic pathway.

3.4.2a Nucleophilic side chain cleavage employing LiOH.

A commonly used cleavage technique of *N*-acyl-oxazolidin-2-ones is basic hydrolysis to afford their corresponding carboxylic acids.[53] However, the use of small, hard nucleophiles such as LiOH and NaOH for these type of hydrolysis reactions has been reported to cause significant endocylic cleavage.[55] To ascertain the sensitivity of our system to endocyclic cleavage, *N*-isovaleryl oxazolidin-2-one functionalised resin **151** (loading 1.10 $mmolg^{-1}$) was treated with varying amounts of LiOH in a THF / D_2O solvent system* for 6 hours. The extent of cleavage was measured in two ways. Firstly, the side chain product (lithium isovalerate **159**) produced was collected *via* filtration of the resin after completion of the reaction and thorough washing with DCM and THF. The washings were evaporated on a cool waterbath and the resulting residue dissolved in D_2O for ^{1}H-NMR analysis. A known amount of crotonic acid was added to the ^{1}H-NMR sample to act as an internal standard to allow accurate quantification of the yields gained *via* comparison of appropriate intergrals. In addition, the residual LiOH-cleaved resin was subsequently treated with TFA in order to cleave the remaining auxiliary fragment. This approach enabled quantification of any *N*-isovaleryl-oxazolidin-2-one **154** and *N*-H oxazolidin-2-one **1** present, as well as enabling identification of any *N*-acyl-β-amino alcohol **161** formed by the endocyclic cleavage pathway.

* It should be noted that polar, non-swelling solvents such as water can be used as part of a mixed solvent system with polystyrene resins but must be used in conjunction with a swelling solvent. (80)



Scheme 3.4.2a: *Nucleophilic cleavage of N-isovaleryl-oxazolidin-2-one* **151** *using LiOH, to form desired exocyclic cleaved products* **2** *and* **159**, *and unwanted endocyclic cleaved product* **160**. *Resulting resin then treated with 1% TFA to remove the auxiliary fragment and to establish extent and nature of cleavage.*

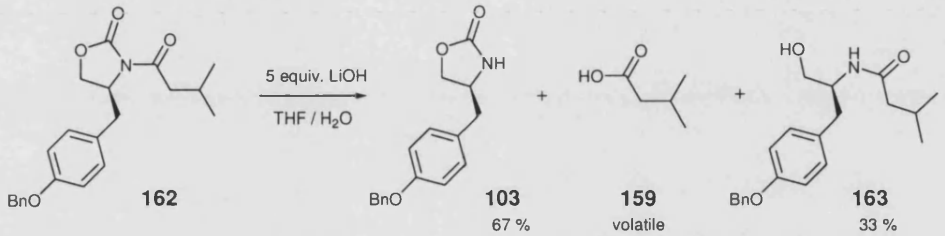
To allow accurate determination of the ratio of the three possible species, **154**, **1** and **161** formed in this TFA cleavage reaction, it was necessary to use d_3-MeCN as a solvent for ^{1}H-NMR studies, since it enabled full solvation of the whole sample and resulted in ^{1}H-NMR spectra with non-overlapping characteristic peaks for each component.

LiOH used	Yield of Acid [a] (%)	Ratio[b] **154** : **1** : **161**
2 equiv.	21	7 : 2.5 : 0.5
5 equiv.	45	2 : 6.2 : 1.8
10 equiv.	70	0 : 7.2 : 2.8

Table 3.4.2a: *Investigation of LiOH-mediated side chain cleavage of polymer-supported N-Isovaleryl oxazolidin-2-one auxiliary* **151**. [a] *Isolated yield determined by ^{1}H-NMR in d_3-MeCN with 0.025 mmol crotonic acid as internal standard, based upon previously determined loading of functionalised N-Isovaleryl oxazolidin-2-one resin.* [b] *Ratio of products observed after TFA cleavage of remaining resin-bound auxiliary fragment after LiOH treatment.*

It was found that 10 equiv. LiOH was required to ensure complete cleavage of the isovaleryl side chain so that no isovaleryl-oxazolidin-2-one **154** was recovered after the cleavage reaction. However, at these concentrations, there was clearly a high incidence of the undesirable endocyclic cleavage pathway occurring, with the identity of *N*-acyl-β-amino alcohol product **161** being confirmed after isolation *via* column chromatography,

characterisation by ^{1}H- and ^{13}C-NMR analysis and comparison against similar literature compounds. Solution phase studies, employing *O*-benzyl-protected auxiliary **162** showed that the use of a large excess of LiOH (5 equivs.) also caused a significant degree of exocyclic cleavage in solution phase, with 33% of endocyclic cleavage product *N*-isovaleryl-β-amino alcohol product **163** being recovered (see Scheme 3.4.2a*ii*).



Scheme 3.4.2a*ii*: *Exocyclic cleavage of solution phase oxazolidin-2-one* **162** *upon treatment with 5 equiv. LiOH for 6 h at rt.*

It was clear therefore, that LiOH cleavage was not suitable as a nucleophile to cleave this polymer as the significant presence of the endocyclic pathway would result in low yields of the desired acid and also result in destruction of the oxazolidin-2-one ring system thus rendering the polymer non-recyclable.

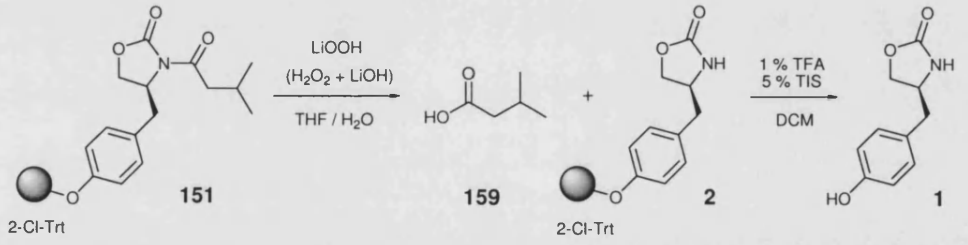
Alternative cleavage systems have been developed to circumvent this endocyclic cleavage problem. For example, lithium hydroperoxide (LiOOH) has been reported to hydrolyse the exocyclic amide functionality of *N*-acyl-oxazolidin-2-ones selectively under similar conditions (LiOOH, THF / H_2O) with no endocyclic cleavage occurring.[55] Consequently, we next explored the use of LiOOH as an alternative nucleophile for cleavage of our polymer supported oxazolidin-2-one.

3.4.2b Nucleophilic cleavage of N-acyl-oxazolidin-2-ones using LiOOH.

Nucleophilic cleavage with lithium hydroperoxide (LiOOH) has been reported to cause no endocyclic cleavage of *N*-acyl-oxazolidin-2-ones [55] and has consequently been used extensively in solution phase for this purpose. The reasons for the insensitivity of LiOOH to steric hindrance in carboxamide hydrolysis are not fully understood, but may be related

to the alpha effect which is responsible for the enhanced nucleophilicity of HOO^- compared to HO^-.[81] It may also be due to the smaller size of the HOO^- anion in solution making it less prone to steric effects.

Phoon *et al.* had commented that the use of LiOOH to cleave an acyl side chain from a Wang-resin supported aldol product had resulted in the cleavage product being "heavily contaminated with unidentified impurities".[32] Therefore, a sample of un-derivatised 2-chlorotrityl-chloride resin was treated with 5 equivalents of LiOOH in THF / H_2O (8:1) at 0 °C to rt over 18 hours. After removal of the filtrate, thorough washing of the polymer support (DCM, DCM/MeOH, MeOH) and evaporation of the combined organic extracts, no significant impurities were found. Treatment of *N*-H oxazolidin-2-one functionalised resin in a similar manner also showed no sign of decomposition products being formed. Therefore, *N*-isovaleryl oxazolidin-2-one functionalised resin **151** was treated with LiOOH under the same conditions to afford isovaleric acid **159** in an acceptable 65% yield. Subsequent cleavage of the residual LiOOH-treated resin with TFA revealed that complete endocyclic cleavage of the acyl fragment had occurred with only *N*-H auxiliary **1** being observed in the ^{1}H-NMR spectrum and no sign of any endocyclic cleavage having occurred. Therefore, these LiOOH cleavage conditions had resulted in no endocyclic cleavage.

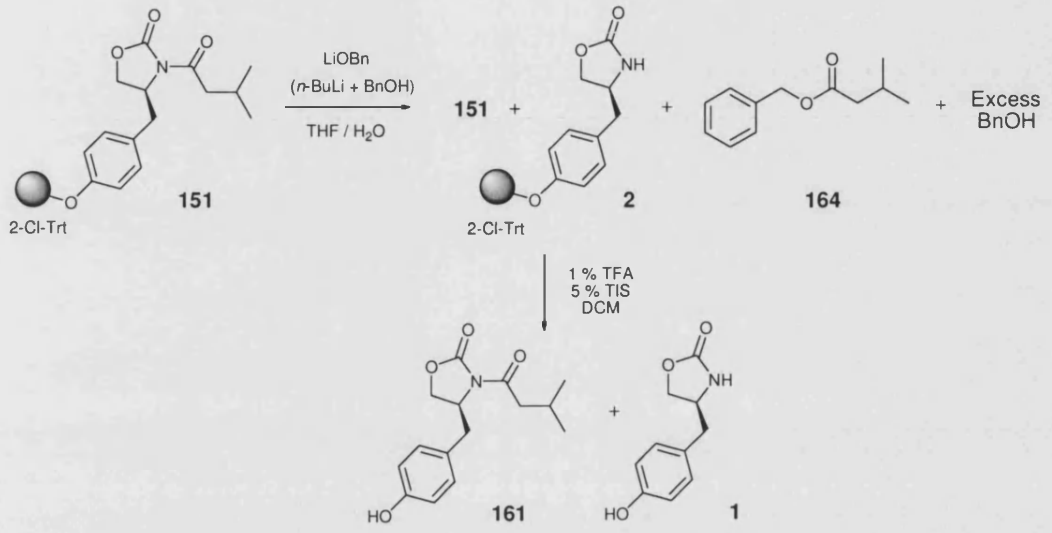


Scheme 3.4.2b: *Nucleophilic cleavage of N-isovaleryl-oxazolidin-2-one* **151** *using LiOOH, to form the desired exocyclic cleaved products* **159** *and* **2** *with no sign of any unwanted endocyclic cleavage. Resulting resin then treated with 1% TFA to remove the auxiliary fragment and to establish extent and nature of cleavage.*

3.4.2c Nucleophilic side chain cleavage of N-acyl-oxazolidin-2-ones using LiOBn.

Cleavage of the side chain of chiral *N*-acyl-oxazolidin-2-ons using LiOBn has been reported to proceed in good yields, with no endocyclic cleavage and no racemisation

occurring.[51] LiOBn was generated in-situ (*n*-BuLi (5 equiv.) + BnOH (6 equiv.)), and added to functionalised *N*-Isovaleryl resin **151** (1 equiv.) at 0 °C followed by stirring at rt for 18 h.



Scheme 3.4.2c: *Nucleophilic cleavage of N-isovaleryl-oxazolidin-2-one* **151** *using LiOBn, to form desired exocyclic cleaved products* **2** *and* **164**, *with no sign of any unwanted endocyclic cleavage occurring. Resulting resin then treated with 1% TFA to remove the auxiliary fragment and to establish extent of cleavage.*

Upon completion of the reaction, the resin was washed thoroughly and all washings collected and evaporated. Unfortunately, the resultant ^{1}H-NMR spectra were dominated by the presence of excess benzyl alcohol and hence reliable yields based on mass recovery could not be calculated. However addition of a known amount of crotonic acid to the ^{1}H-NMR sample as an internal standard did allow the isolated yield to be estimated for reactions involving 1.5 and 2.5 equivalents LiOBn. However, the amount of BnOH present in the reaction involving 5 equivalents LiOBn was too great to allow any useful interpretation of the ^{1}H-NMR spectrum and in this case, column chromatography was used to isolate the benzyl ester **164** in 79% yield.

Fortunately, the success of the cleavage reaction could also be monitored by examining the ratio of oxazolidin-2-one fragments produced on TFA cleavage from polymer support. Again, it was found that an excess of LiOBn (5 equiv.) was required to cause complete endocyclic cleavage of the acyl fragment from polymer support.

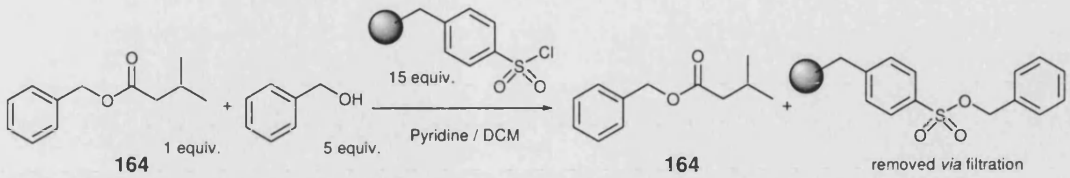
LiOBn used	Yield of Ester **164** [a]%	Ratio[b] **1** : **161**
1.5 equiv.	43	1 : 1
2.5 equiv.	54	1 : 0.6
5.0 equiv.	79[c]	1 : trace

Table 3.4.2c: *Investigation of LiOBn-mediated side chain cleavage of polymer-supported N-isovaleryl oxazolidin-2-one auxiliary* **151**. [a] *Isolated yield determined by ^{1}H-NMR in d_3-MeCN using crotonic acid as an internal standard, based upon the initial loading of functionalised N-isovaleryl oxazolidin-2-one resin* **151**. [b] *Ratio of products observed after TFA cleavage of residual resin-bound auxiliary fragment after LiOBn treatment.* [c] *Isolated yield after column chromatography to remove excess BnOH.*

In order for this LiOBn cleavage method to be useful, it was necessary to develop a method for removing the excess benzyl alcohol from the ester product after the cleavage reaction was complete. The high boiling point of benzyl alcohol (205 °C) renders evaporation conditions reasonably harsh, raising concerns about the volatility and thermal stability of the product ester. Also, benzyl alcohol is not sufficiently aqueous soluble to allow complete removal by successive washing, even as its alkoxide. As had been shown, removal of residual benzyl alcohol could be easily achieved by column chromatography however it was our aim to make the whole process of synthesis and purification as amenable to automated systems as possible. Hence a generic, universal purification method was desired.

Consideration of the protecting group chemistry of benzyl alcohol led to the development of a technique to remove the excess benzyl alcohol *via* the use of a solid-phase scavenging resin. In solution phase, benzyl alcohol can be protected as its tosylate by treatment with tosyl chloride in the presence of pyridine. It was therefore reasoned that addition of an excess of polymer-supported tosyl chloride and pyridine to the crude reaction product arising from the LiOBn cleavage reaction, would result in scavenging of the benzyl alcohol by the tosyl chloride resin. [66] Any remaining pyridine could then be easily removed *via* an acidic wash, or *via* evaporation *in vacuo* (pyridine b.p 115 °C). Hence, the LiOBn cleavage reaction was repeated according to the method described above where 5 equivalents of LiOBn (prepared from *n*-BuLi (5 equiv.) and BnOH (6 equiv.) in THF), was added to *N*-isovaleryl resin **151**(1 equiv.). After 18 hours, the resin was washed thoroughly with DCM and THF and the solvent removed *in vacuo*. The resulting oily residue was redissolved in DCM and pyridine (2:1) and ps-tosyl chloride resin (loading 2.4 mmolg^{-1})(3 equivs. with

respect to BnOH) added and the whole reaction mixture agitated at room temperature for 12 hours on an orbital shaker (see Scheme 3.4.2*cii*).



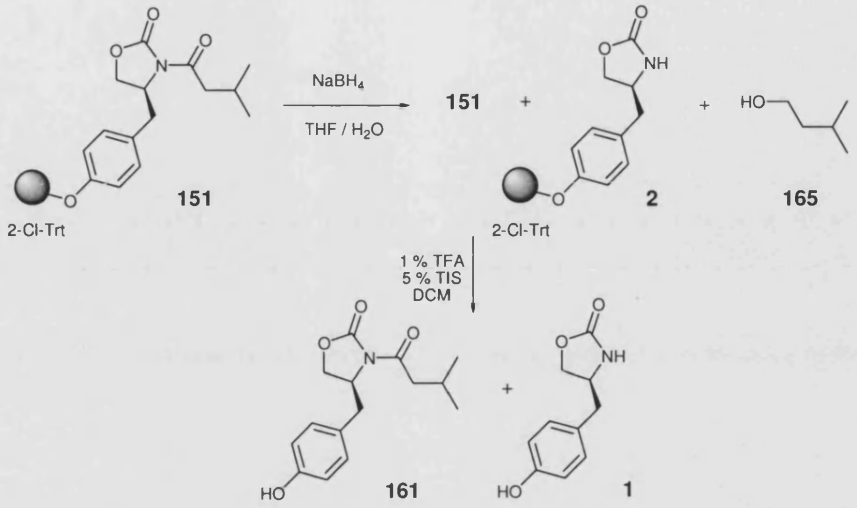
Scheme 3.4.2*cii* : *Solid phase scavenging of excess BnOH by ps-tosyl chloride after LiOBn cleavage.*

After filtration of the resin and thorough washing with DCM, the organic layer was washed with 1.0 N HCl and brine and solvent removed *in vacuo* to yield benzyl ester **164** in good yield (81%) and in excellent purity with no traces of either benzyl alcohol or pyridine remaining.

It was anticipated that this scavenging method would also be applicable to the cleavage of chiral esters from polymer support since pyridine is a weak base that would not cause racemisation of the side-chain stereocentre.

3.4.2d Reductive cleavage of N-acyl-oxazolidin-2-ones using $NaBH_4$.

In solution phase, reductive cleavage of *N*-acyl oxazolidin-2-ones with sodium borohydride ($NaBH_4$) has been reported to proceed with no racemisation to afford their corresponding alcohols in good yield.[56] Hence, polymer-supported *N*-Isovaleryl oxazolidin-2-one resin **151** was treated with $NaBH_4$ (5 equiv.) in THF/H_2O (4:1) solution over a period of 18 hours.



Scheme 3.4.2d: *Nucleophilic cleavage of N-isovaleryl-oxazolidin-2-one* **151** *using* $NaBH_4$*, to form desired exocyclic cleaved products* **2** *and* **165***, with no sign of any endocyclic cleavage occuring. Resulting resin then treated with 1% TFA to remove the auxiliary fragment and to establish extent of cleavage.*

Unfortunately, upon filtration of the resin and evaporation of the washings, 3-methyl-butan-1-ol **165** could not be isolated, presumably due to its inherent volatility (b.p. 130 °C) that lead to its loss on solvent evaporation. However, cleavage of the remaining resin with 1% TFA in DCM revealed the exclusive formation of *N*-H oxazolidin-2-one **1** suggesting that reductive side-chain cleavage had proceeded quantitatively and that no endocyclic cleavage had occurred.

3.4.2e Nucleophilic side chain cleavage – conclusions

The preceeding sections have described the development of three methods of side-chain cleavage, employing LiOOH (to produce carboxylic acids), LiOBn (to prepare benzyl ethers) and $NaBH_4$ (to prepare alcohols). In each case the reaction conditions have been optimised to ensure complete side-chain removal and in each case there was no sign of the competing endocyclic cleavage pathway acting to destroy the oxazolidin-2-one ring. However, yields of the side-chain cleaved products were disappointingly low (with the exception of the ester product obtained from LiOBn cleavage). It is anticipated that this is due to problems isolating the small, volatile and water-soluble compounds, and thus yields

should be improved in a real reaction scenario where the asymmetric reaction would have increased the mass of the side-chain product. Each of the three methods has its merits and as such, it was decided to test and compare all three methods for the nucleophilic side-chain cleavage of the resin resulting from a polymer-supported asymmetric reaction (see Chapter 4).

3.5 Summary

In this chapter, the fundamental synthetic protocols for the development of a solid-supported chiral auxiliary have been established. Commercially available 2-chlorotrityl-chloride functionalised polystyrene resin was selected as a low-cross-linked polystyrene support with an acid-labile linker already pre-attached. The use of an acid-labile linker was designed to allow orthogonal cleavage of key-solid supported intermediates by offering an alternative cleavage site to the nucleophilic *N*-acyl-side-chain cleavage traditionally used in oxazolidin-2-one chemistry. It was anticipated that this approach would greatly facilitate characterisation of side-products and intermediates and therefore aid optimisation of reaction conditions for future solid-supported asymmetric reactions.

Reaction conditions for the immobilisation of oxazolidin-2-one auxiliary fragments onto 2-chlorotrityl-chloride polystyrene resin were then established and functionalised resins of reasonable loading (approx. 1 $mmolg^{-1}$) have been achieved. In addition, various methods of *N*-acylating the polymer-supported oxazolidin-2-one were established, allowing a range of *N*-acyl-oxazolidin-2-ones to be prepared 'on-bead'.

Finally, four different methods of cleaving polymer-supported *N*-acyl-oxazolidin-2-ones have been optimised. Firstly, treatment of the resin with 1% TFA results in cleavage of the entire oxazolidin-2-one fragment with its *N*-acyl side-chain intact. Alternatively, three different methods to effect nucleophilic cleavage of the *N*-acyl side chain from the polymer-supported oxazolidin-2-one were developed, each proceeding efficiently and with no sign of any endocyclic cleavage occurring.

With reliable conditions for these fundamental reactions in hand, it was now possible to begin the development of efficient polymer-supported oxazolidin-2-one-mediated asymmetric reactions, as will be discussed in Chapters 4 and 5

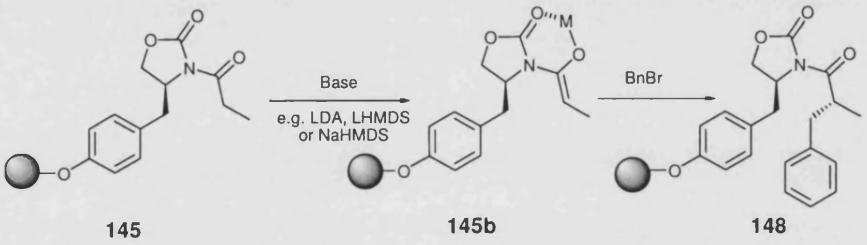
Chapter 4 Solid phase asymmetric enolate alkylations.

4.1 Introduction

In the preceding chapter, reaction conditions were developed and optimised to allow fundamental reactions essential to the development of a polymer-supported chiral auxiliary to be conducted. These consisted of immobilisation of the chiral auxiliary onto polymer support, *N*-acylation of the solid-supported oxazolidin-2-one and orthogonal cleavage of the acid-labile linker attaching the oxazolidin-2-one fragment to the resin as well as conventional side-chain cleavage of the *N*-acyl fragment. These reactions constituted the basic tools necessary to develop solid-supported asymmetric reactions, commencing with the solid-supported asymmetric enolate alkylation protocol described in this chapter.

4.2 Characterisation

A typical reaction for the exploration of the potential of an Evans oxazolidin-2-one type chiral auxiliary is the asymmetric alkylation of the enolate of its *N*-propionyl derivative (see Scheme 4.2a). As discussed in Chapter 2, this model reaction was investigated and optimised in solution phase and it was therefore planned to apply these findings to the corresponding solid phase system.



Scheme 4.2a: *Model transformation to be investigated: alkylation of the enolate of solid-supported N-propionyl oxazolidin-2-one* **145** *with benzyl bromide.*

Before attempting to perform asymmetric enolate alkylation reactions on oxazolidin-2-one functionalised resin **2**, it was deemed wise to prepare authentic samples of the reaction products using conventional solution phase chemistry (see Fig. 4.2a). This would allow unambiguous identification of species in potentially complex mixtures of crude reaction products since solution phase studies had suggested up to five structurally similar compounds could be formed in this type of enolate alkylation reaction.

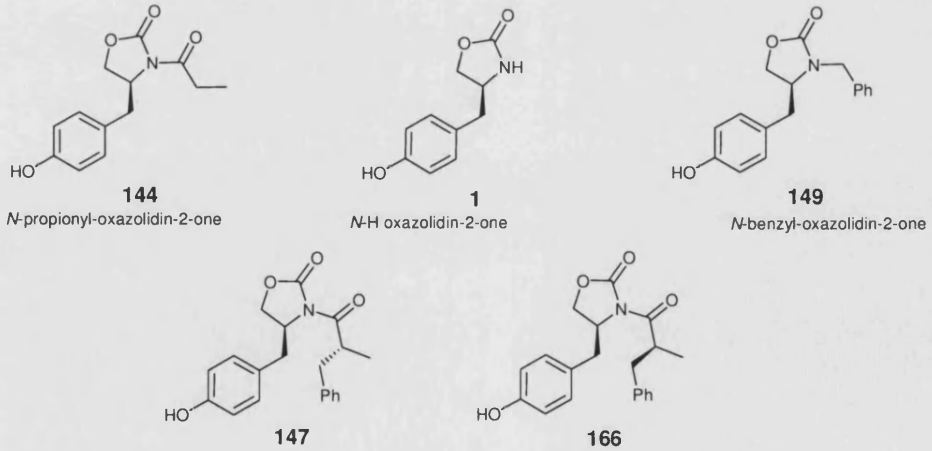
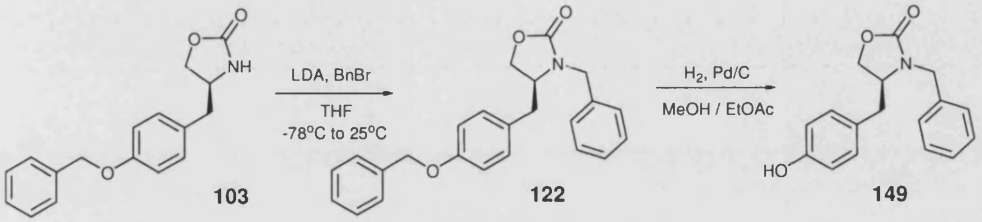


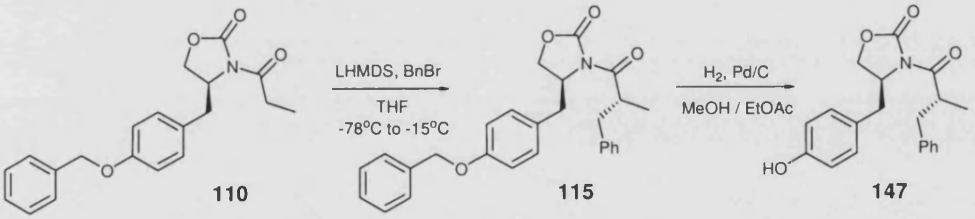
Fig 4.2a: *Potential products of solid phase enolate alkylation reaction of N-propionyl-oxazolidin-2-one* **145** *with benzyl bromide after TFA cleavage.*

N-H oxazolidin-2-one **1** and *N*-propionyl oxazolidin-2-one **144** had been prepared previously and characterised (see Chapter 3). *N*-benzyl oxazolidin-2-one **149** was prepared by catalytic hydrogenation of *N*-benzyl auxiliary **122**, which had been formed by treatment of *N*-H oxazolidin-2-one **103** with LDA and benzyl bromide (see Scheme 4.2b).



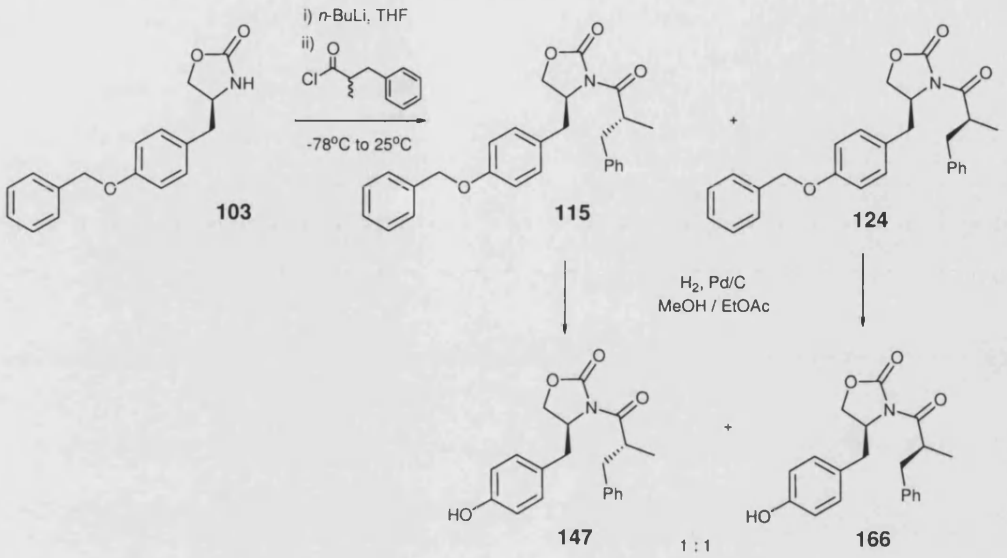
Scheme 4.2b: *Preparation of* **149** *via solution phase alkylation of the enolate of N-H oxazolidin-2-one* **103** *and subsequent catalytic hydrogenation of* **122** *to remove the benzyl ether protecting group.*

Similarly, the major diastereomeric product of the enolate alkylation reaction **147** was prepared by catalytic hydrogenation of its parent *O*-benzyl-product **115** (again prepared in solution phase) (see Scheme 4.2c).



Scheme 4.2c: *Preparation of* **147** *via solution phase asymmetric alkylation of the enolate of N-acyl oxazolidin-2-one* **110** *and subsequent catalytic hydrogenation of* **115** *to remove the benzyl ether protecting group.*

A 1:1 mixture of **147**and **166** was achieved by acylation of *N*-H auxiliary **103** with racemic 2-benzylpropanoic acid that was converted to its acid chloride *in situ via* refluxing with thionyl chloride in DCM (see Chapter 5.1 for details), followed by catalytic hydrogenation of the 1:1 mixture of *N*-acyl-oxazolidin-2-one diastereomers **115** and **124** (see Scheme 4.2d). No attempts were made to separate the resulting two diastereomers since the peaks corresponding to **166** in the ^{1}H-NMR spectrum of a 1:1 mixture of **147** and **166** could easily be identified by comparison with the ^{1}H-NMR spectrum of a pure sample of **147** (For details and copy of spectrum see Fig 4.2.2a and associated text).



***Scheme 4.2d**: Preparation of a 1:1 mixture of* **147** *and* **166** *via solution phase acylation of N-H oxazolidin-2-one* **103** *with rac-2-benzylpropanoyl chloride and subsequent catalytic hydrogenation of a 1:1 mixture of* **115** *and* **124** *to remove the benzyl ether protecting group.*

In order to develop optimal conditions for the solid-supported enolate alkylations, it was proposed that three aspects of the reaction would need to be monitored. Firstly, the composition of the crude product mixture would have to be established, with the ultimate aim of achieving a high conversion of starting *N*-propionyl oxazolidin-2-one **144** to α-benzylated product **147** with minimal formation of the two decomposition products *N*-H-oxazolidin-2-one **1** and *N*-benzyl-oxazolidin-2-one **149**. Secondly, the extent of the system's diastereoselectivity would need to be determined by measurement of the de of the α-benzylated product **147** by HPLC (after cleavage of an aliquot of resin with TFA). Finally, the *e.e.* of the side-chain cleaved product as its carboxylic acid, alcohol or benzyl ester would need to be determined, again by HPLC. It should be noted that the latter two methods should result in identical numerical values since the side-chain cleavage methods proposed were reported to be non-racemising and therefore the ee should be a direct consequence of the *de*. However, it was decided to measure and compare both values against each other as a safeguard against any unforseen epimerisation / racemisation events caused by the presence of the polymer support.

4.2.1 Determination of crude product mixture composition

Determination of the composition of the crude product mixture required a rapid, high-throughput method of analysis. Initially ^{1}H-NMR spectroscopy was proposed as a potential method, however, the structural similarity of the species produced in the crude reaction product afforded a complicated spectrum with overlapping signals that were difficult to interpret. However, analysis of the crude product of TFA cleavage by LC/MS gave good separation of the product peaks with the exception of the two diastereomers of the α-alkylated product which were resolved but did not quite achieve baseline separation.*
This analytical approach also had the advantage of allowing accurate characterisation of each compound peak by mass-spec analysis and could be performed on a small quantity of crude product (1 mg). Concurrent analysis of the same sample on a LC/UV instrument (same solvent system) allowed quantitative analysis of the mixture composition after calibration to account for differences in the UV chromophore of the acyl substituent of each of the components (see Appendix).

4.2.2. Determination of d.e.

A crucial aspect of this investigation was the accurate determination of the diastereoselectivity of the asymmetric reaction. Preparation of both possible diastereomers (**147** and **166**) *via* solution phase synthesis allowed conditions for this determination to be developed. ^{1}H-NMR analysis of a 1:1 mixture of the two diastereomers (**147** and **166**) revealed that a number of their resonances were coincident. However, there were some characteristic differences between the two spectra that were diagnostic, notably the C*H*N multiplets at δ 4.40 ppm and 4.55 ppm (see Fig. 4.2.2a).

*3μm ABZ+ column, Solvent systems used were 0-100% gradient of 0.1% formic acid +10mM ammonium acetate and 95% acetonitrile + 0.05% formic acid. *N*-H oxazolidin-2-one **1** (t_R = 1.7 min), *N*-propionyl oxazolidin-2-one **144** (t_R = 2.4 min), *N*-benzyl oxazolidin-2-one **149** (t_R = 2.7 min), α-benzylated product, major diastereomer **147** (t_R = 3.05 min), α-benzylated product, minor diastereomer **166** (t_R = 3.10 min).

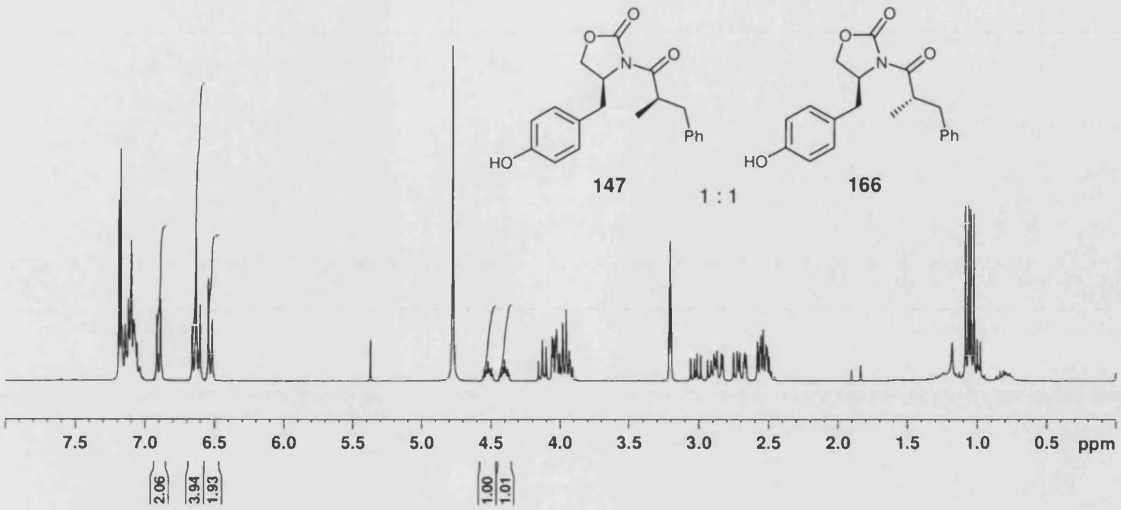


Fig. 4.2.2a: *^{1}H-NMR of a 1: 1 mixture of diastereomers* **147** *and* **166** *in d_4-MeOD.*

However, again there were concerns that these resonances might be coincident with resonances of other reaction products present in the complicated crude reaction product spectrum, particularly as the high de's expected would make the minor diastereomer signals very weak in comparison with those of the major diastereomer. Therefore, an additional method, allowing greater sensitivity was sought. As previously discussed, the available open-access LCMS/LCUV system did not achieve baseline separation between the two peaks, with the major diastereomer peak that eluted first tailing into the minor diastereomer peak which made the de value obtained appear considerably lower than it actually proved to be.*

A normal-phase HPLC method was therefore developed to separate the two diastereomers of the α-benzylated product; with a ChiralCel AD column resulting in excellent separation (90% hexane, 10% propan-2-ol, 1 mL per min, major diastereomer **147** t_R = 15 min, minor diastereomer **166** t_R = 23 min). In fact, this ChiralCel column afforded good separation of all compounds present in the crude reaction mixture.† However, it must be noted that this method could not be used to quantitatively ascertain the composition of the crude mixture

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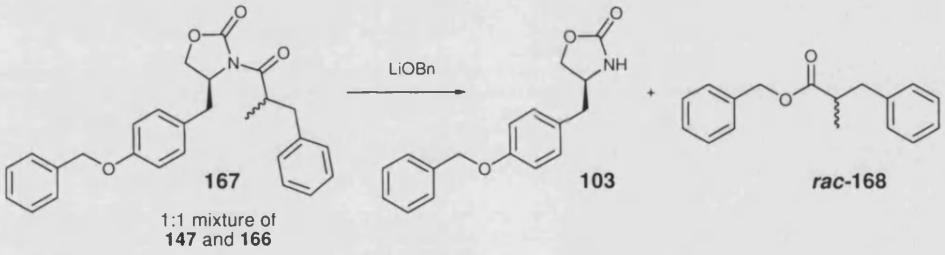
* Analysis of 1:1 mixture of **147**and **166** by this method gave *d.e.*errors of 15% in favour of the second eluting minor diastereomer.

† α-benzylated product (major diastereomer) **147** t_R = 15 min, α-benzylated product (minor diastereomer) **166** t_R = 23 min, *N*-propionyl oxazolidin-2-one **144** t_R = 26 min, *N*-benzyl oxazolidin-2-one **149** t_R = 38 min, *N*-H oxazolidin-2-one **1** t_R = 50 min.

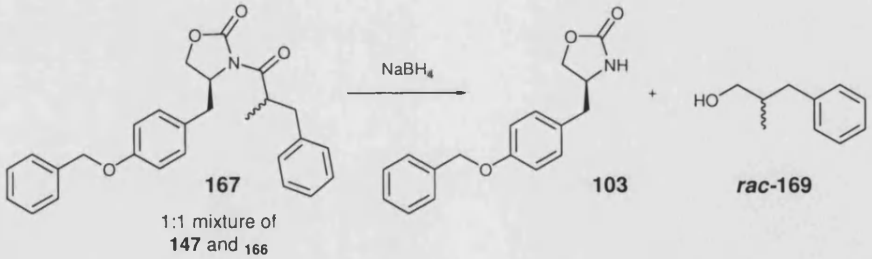
due to poor solubility of the *N*-H oxazolidin-2-one **1** in the eluent which resulted in removal of a significant quantity upon filtration prior to injection onto the column.

4.2.3 Determination of e.e.

Authentic racemic samples of the side-chain cleaved products were prepared by cleavage (using the appropriate nucleophile) of solution phase alkylated product **167** and separation of the product from the auxiliary by column chromatography. Hence a 1:1 mixture of diastereomers **147** and **166** was cleaved with LiOBn to give racemic benzyl-2-benzylpropanoate ***rac*-168** (see Scheme 4.2.3a), and by $NaBH_4$ to give racemic 2-methyl-3-phenylpropan-1-ol ***rac*-169** (see Scheme 4.2.3b) Cleavage of the resin with LiOOH cleavage was not necessary since the acid product 2-benzylpropionic acid was commercially available in its racemic form.



Scheme 4.2.3a: *Preparation of an authentic sample of racemic benzyl-2-benzylpropanoate* ***rac*-168** *via solution phase cleavage of* **167** *with LiOBn.*



Scheme 4.2.3b: *Preparation of an authentic sample of racemic 2-methyl-3-phenylpropan-1-ol* ***rac*-169** *via solution phase cleavage of* **167** *with* $NaBH_4$.

Chiral HPLC conditions were then developed to achieve baseline separation of the enantiomers of each of the compounds (see Table 4.2.3a).

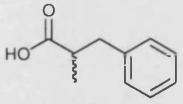
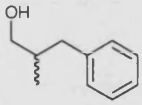
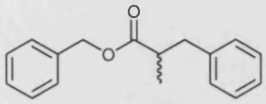
Side-chain product	*Column and eluent*	*Enantiomer 1 (t_R) (min)*	*Enantiomer 2 (t_R) (min)*
 **rac-65**	ChiralCel OJ column 98% hexane, 2% propan-2-ol (with 0.1% TFA), 1 mL min^{-1}	9.5 *	10.8
 **rac-169**	ChiralCel OD column 97% hexane, 3% propan-2-ol 1 mL min^{-1}	10.3	12.8 *
 **rac-168**	ChiralCel OJ-R column ** 60% MeCN, 40% H_2O 0.5 mL min^{-1}	15.7	18.3

Table 4.2.3a: *HPLC conditions for determination of e.e. of side-chain cleaved products. Where known, * indicates enantiomer later identified as the major enantiomer.* ** **rac-168** *had poor retention on normal-phase systems so was analysed on a reverse-phase system – method developed at GlaxoSmithKline, Stevenage by Eric Hortense.*

Analytical techniques required to develop optimal conditions for a polymer-supported asymmetric enolate alkylation had therefore now been established.

To summarise:

1) The composition of the crude product mixture arising from cleavage of the entire *N*-acyl-oxazolidin-2-one fragment from the alkylated resin using 1% TFA, could be established by simultaneous LCMS and LC-UV analysis that enabled compound characterisation and quantification respectively.

2) The de of the alkylated product could be determined *via* HPLC analysis of the crude reaction mixture arising from cleavage of the entire oxazolidin-2-one fragment from the alkylated resin using 1% TFA.

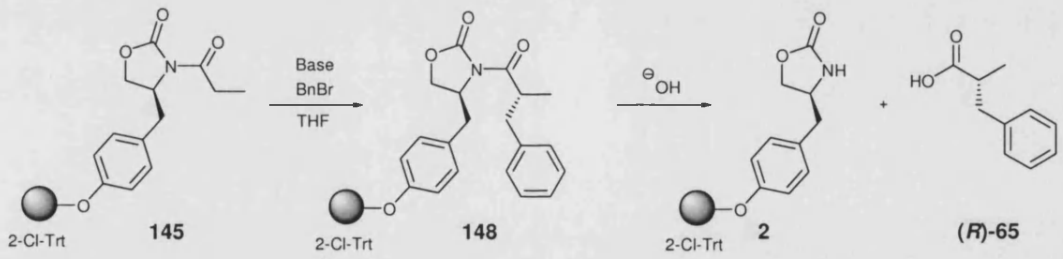
3) The ee of alkylated products could be determined *via* HPLC analysis of the products arising from nucleophilic cleavage of the *N*-acyl side-chain from polymer support using LiOOH, LiOBn or $NaBH_4$.

The optimal method of side chain cleavage was not firmly established before the start of the enolate alkylation optimisation process. Conditions for three different cleavage reactions

were established (see Chapter 3.4.2) but the use of LiOBn (generated from *n*-BuLi and benzyl alcohol) for library development was ruled out at an early stage due to the additional step necessary to remove the excess benzyl alcohol after reaction. Additionally, the reverse-phase HPLC required to determine the ee of the benzyl ester products produced by LiOBn cleavage was not readily available at Bath. Both the LiOOH and $NaBH_4$ cleavage methods were shown to be suitable for our purposes with the carboxylic acid products formed from LiOOH cleavage being easily purified by acidic aqueous extraction, whilst the $NaBH_4$ method was more convenient to carry out at ambient temperature. It was anticipated that any issues arising from volatility and/or water solubility of the side chain cleavage products would be reduced by the extra mass of the electrophile introduced in the actual alkylation reaction. It was therefore decided that the efficiency of each method would be compared for the cleavage of an actual solid-supported enolate alkylation reaction product.

4.3 Optimisation of reaction conditions using model system

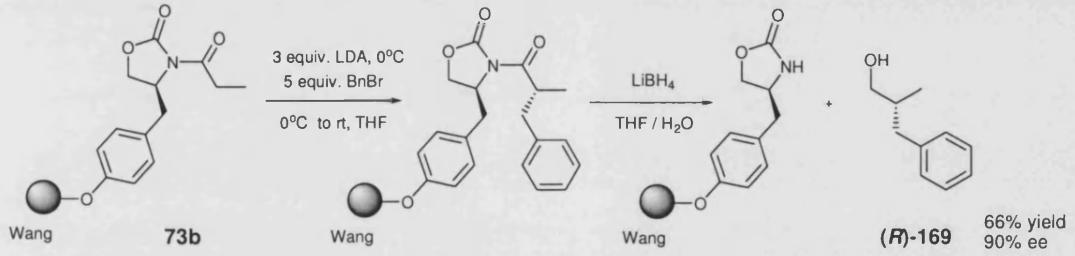
As previously discussed, a typical transformation to explore the potential of a chiral auxiliary for asymmetric enolate alkylation reactions involves treatment of the enolate of polymer-supported *N*-propionyl auxiliary with benzyl bromide (see Scheme 4.3a).[25,53,82]



Scheme 4.3a: *Model transformation to be investigated: alkylation of the enolate of solid-supported N-propionyl oxazolidin-2-one* **145** *with benzyl bromide, followed by nucleophilic side chain cleavage. (Base typically LDA, LHMDS or NaHMDS).*

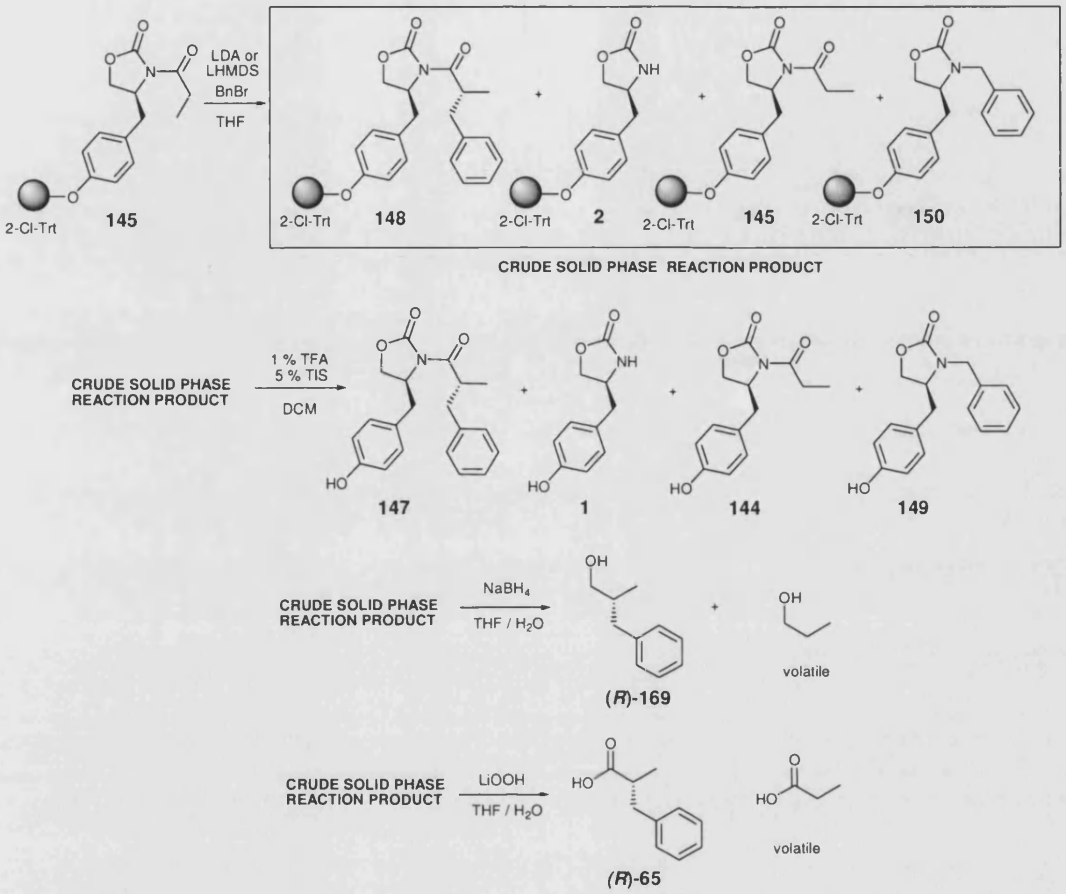
i) Variations of existing literature method

At the time of commencing this work, only one reliable report of the application of a solid-supported oxazolidin-2-one chiral auxiliary for enolate alkylation reactions had been published.[25] Employing the model transformation described above, Burgess *et al.* reported the use of a Wang-supported oxazolidin-2-one **73b** for the preparation of chiral alcohol **(*R*)-169** in 66% yield (for both the alkylation and $LiBH_4$ steps) and 90% ee (see scheme 4.3b).



Scheme 4.3b: *Burgess' enolate alkylation of solid-supported N-propionyl oxazolidin-2-one* **73b** *with benzyl bromide and subsequent $LiBH_4$ cleavage to afford alcohol* **(*R*)-169**.

These conditions were therefore used as a starting point for our investigation. Hence, our 2-chlorotrityl polymer supported oxazolidin-2-one **145** was treated with 3 equivalents of freshly prepared LDA and 5 equivalents of benzyl bromide. However, in our hands, disappointing results were achieved (see Table 4.3a, entry 1) with TFA cleavage affording a sample comprised of 26% unreacted *N*-propionyl oxazolidin-2-one **144**, 33% alkylated product **147** and 41% *N*-H-oxazolidin-2-one **1**. Due to the complex nature of the diastereomeric products cleaved from the resin, a poor isolated 28% yield of alcohol **(*R*)-169** was recovered after $NaBH_4$ side-chain cleavage of the alkylated resin. The stereocontrol achieved (85% de for **147**, 90% ee for **(*R*)-169**) was comparable to that reported by Burgess for **(*R*)-169** of 90% ee. Importantly, the two values determined for the de and ee were comparable with each other, when allowances were made for statistical errors between the two different methods of analysis.



Scheme 4.3c: *Solid phase enolate alkylation of 150 mg of solid-supported N-propionyl oxazolidin-2-one* **145**, *with subsequent cleavage of a 20 mg portion of resin with 1% TFA and 5% TIS in DCM to give crude reaction products that were analysed via LC/UV and HPLC analysis to determine product composition and de respectively. Remaining 120 mg alkylated resin treated with either $NaBH_4$ to give alcohol* **(*R*)-169**, *or LiOOH to give acid* **(*R*)-65**, *with the ee of chiral products being determined by chiral HPLC.*

Entry	Reaction conditions[a]		Crude product from TFA cleavage composition (%) [b]				De of **147** [c] (%)	Method [d], yield [e] and ee [f] of chiral side chain product
	Base	Temp	α-Benzyl **147**	*N*-H **1**	*N*-prop **144**	*N*-benzyl **149**		
1	LDA (3 equiv.)	0 °C	33	41	26	0	85	(*R*)-**169** ($NaBH_4$) 28% yield (90% ee)
2	LDA (3 equiv.)	0 °C [g] (4 hrs)	18	48	8	26	51	Not cleaved [h]
3	LHMDS (3 equiv.)	0 °C	64	30	0	6	87	(*R*)-**169** ($NaBH_4$) 52% yield (83% ee)
4	LHMDS (3 equiv.)	- 15 °C	62	15	20	3	85	(*R*)-**65** (LiOOH) 56% yield (83% ee)

Table 4.3a: ***Investigating variations of existing literature methods.***
[a] All reactions (except entry 4) conducted as follows: 3 equiv. of base added to 150 mg pre-swollen resin **145** *in 6 ml dry THF at stated temperature and stirred for 30 min. before addition of 5 equiv. BnBr. Reaction stirred for a further 30 mins at stated temperature then removed from ice-bath and stirred for a further 20 min before quenching. [b] Crude product decomposition determined by LCMS and LC-UV analysis. [c] De determined by HPLC analysis of crude product of TFA cleavage of 20-50 mg portion of resin after alkylation reaction. [d] Side-chain cleavage reaction employed either LiOOH or $NaBH_4$ as nucleophile. [e] Isolated yield after appropriate work-up based upon the calculated loading of N-H oxazolidin-2-one on 2-Cl-Trt resin representing the combined yield over three steps – N-acylation, enolate alkylation and side-chain cleavage. [f] Ee determined by HPLC analysis of side-chain cleaved product after appropriate work-up. [g] Reaction conditions as for a) however after removal of the reaction from an ice-bath, the reaction was stirred for an additional 3 hours at room temperature. [h] Nucleophilic cleavage not undertaken due to poor yields of α-benzylated product* **147**.

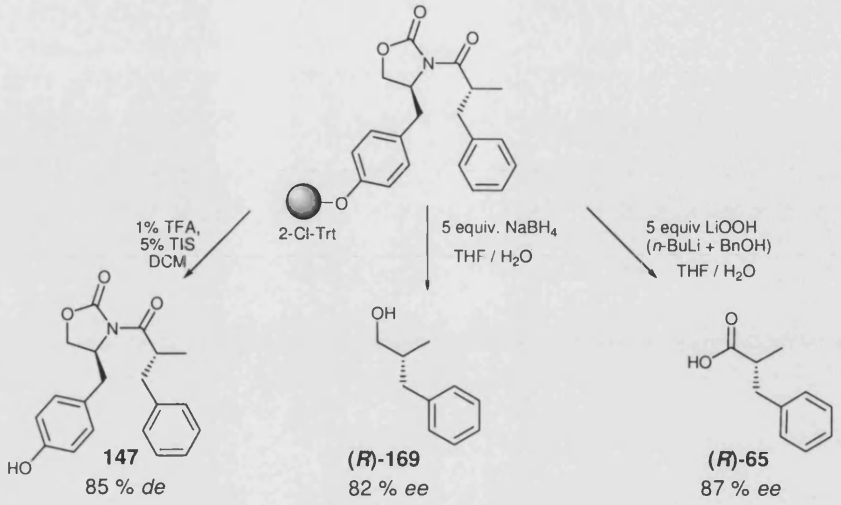
In an attempt to drive the reaction to completion, the enolate alkylation reaction was repeated but left for an extended duration of 4 hours at 0 °C (see Table 4.3a, entry 2). Perhaps unsurprisingly considering our previous solution phase studies, this resulted in extensive enolate decomposition with 48% *N*-H oxazolidin-2-one **1** and 26% *N*-benzyl oxazolidin-2-one **149** being isolated. Both the percentage conversion and de of the alkylated product **147** were poor (18% and 51% respectively).

In solution phase enolate alkylations, LHMDS is often used as an alternative to LDA since LHMDS is commercially available in THF solution and retains its activity on storage. It therefore represented a more convenient and reliable alternative to the *in-situ* preparation of LDA or the use of unreliable commercially available solutions.

Hence the enolate alkylation reaction was repeated following an identical procedure, employing LHMDS as base (see Table 4.3a, entry 3). This was found to achieve superior conversions, with no starting material **144** recovered and 64% α-benzylated product **147** being detected with levels of stereocontrol comparable to that achieved using LDA (87% de, 83% ee of **(*R*)-169** after $NaBH_4$ cleavage). However, once again there was a significant amount of *N*-H oxazolidin-2-one **1** recovered and also some *N*-Benzyl oxazolidin-2-one **149** implying significant enolate decomposition had occurred.

ii) Selection of LiOOH as the preferred method of side-chain cleavage

At this stage it was decided to employ LiOOH cleavage as the preferred method of cleavage of the *N*-Acyl side chain from polymer supported products. Cleavage of the same batch of α-benzylated resin *via* three different methods (see scheme 4.3d) had confirmed that all three cleavage methods had afforded comparable de/ee values for the products obtained. However it was clear that the acidic products resulting from LiOOH cleavage were generally cleaner and easier to analyse than the alcohol products obtained from $NaBH_4$ cleavage, presumably due to the acidic aqueous extraction method used for workup, and as a consequence this method of side-chain cleavage was employed in subsequent optimisation reactions.



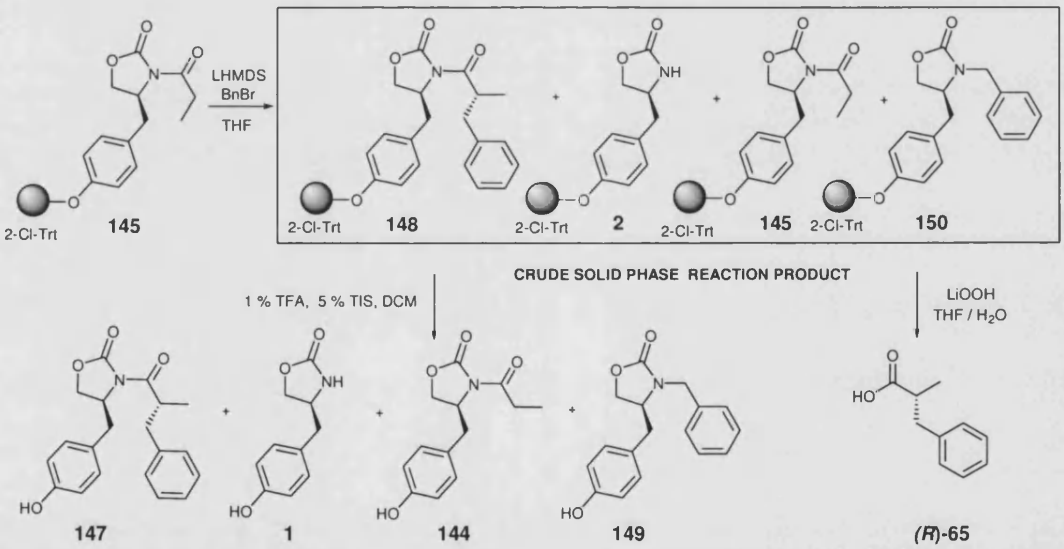
Scheme 4.3d: *Cleavage of α-benzylated resin via three different methods to allow comparison of the de and ee values.*

iii) Reducing the reaction temperature...

From earlier solution phase studies it was known that enolate decomposition of *N*-acyl-oxazolidin-2-ones was temperature dependant, with temperatures above 0 °C causing appreciable decomposition. However, it had been found that such decomposition could be essentially eliminated by keeping the reaction below -15 °C. It was reasoned that the same reduction in temperature might help reduce the decomposition occurring on solid phase systems, and hence the reaction was again repeated, using LHMDS at -15 °C (see Table 4.3a, entry 4). This alteration to the method was partially successful, with fewer decomposition products formed (15% *N*-H-oxazolidin-2-one **1** and 3% *N*-Benzyl oxazolidin-2-one **149**) however, the lower temperature also resulted in a reduced reaction rate with 20% *N*-propionyl oxazolidin-2-one **144** being recovered. Despite this, the conversion to α-benzylated product **147** was comparable to that achieved at 0 °C (table 4.3b, entry 3) which had been formed with similar levels of stereocontrol (85% de and 83% ee after LiOOH cleavage). However, it was clearly desirable to identify conditions that would result in the alkylation reaction proceeding to completion, not only to improve isolated yields of **147** but also because any residual *N*-propionyl oxazolidin-2-one **144** would lose its propionyl side-chain in the subsequent cleavage step and hence contaminate the desired chiral acid product **(*R*)-65**. Although in this model transformation the resulting

propionic acid was volatile and could therefore be removed upon work-up, in other cases where larger *N*-acyl side-chains were employed this would not be the case.

It was therefore necessary to try to identify conditions to drive the enolate alkylation reaction to completion. Maintaining the temperature at -15 °C throughout and employing LHMDS as the base, the reaction duration was increased to 12 hours in an attempt to encourage complete benzylation of all the *N*-propionyl enolate species (see Table 4.3b, entry 1). However, despite all the starting material being consumed, there was a slight decrease in the percentage of α-benzylated product **147** produced as well as a decrease in the diastereoselectivity of the asymmetric enolate alkylation reaction, affording a de of just 74% (70% ee after LiOOH cleavage). Furthermore, significant levels of *N*-H oxazolidin-2-one **1** were again observed indicating the occurrence of significant amounts of enolate decomposition.



Scheme 4.3e: *Solid phase enolate alkylation of 150 mg of solid-supported N-propionyl oxazolidin-2-one* **145**, *with subsequent cleavage of a 20 mg portion of resin with 1% TFA and 5% TIS in DCM to give crude reaction products that were analysed via LC/UV and HPLC analysis to determine product composition and de respectively. Remaining 120 mg alkylated resin treated with LiOOH to give acid* **(*R*)-65**, *with the ee of chiral products being determined by chiral HPLC.*

Entry	Reaction conditions [a]		Composition of crude product from TFA cleavage (%) [b]				De of **147** [c] (%)	Method [d], yield [e] and ee [f] of chiral side chain product
	Equiv. LHMDS	Reaction duration	α-benzyl **147**	*N*-H **1**	*N*-prop **144**	*N*-benzyl **149**		
1	3	2 hr with LHMDS then 12 hr with BnBr.	55	38	0	7	74	**(*R*)-65** 45% yield 70% ee
2	10	30 min with LHMDS, then 80min with BnBr.	66	19	15	0	90	**(*R*)-65** 59% yield 85% ee
3	10	2 hr with LHMDS then 12 hr with BnBr.[g]	57	38	0	5	68	Not cleaved

Table 4.3b: ***Investigating the effect of reducing the reaction temperature, increasing the excess of reagents used and increasing the duration.***

[a] Reaction conducted as follows: Stated equiv. of LHMDS added to 150 mg pre-swollen resin **145** *in 6 mL dry THF at -15 °C and stirred for the stated amount of time before addition of BnBr (when 3 equiv. of LHMDS employed then 5 equiv. of BnBr used, when 10 equiv. of LHMDS employed then 20 equiv. of BnBr used). Reaction stirred for a further stated period of time at -15 °C then quenched. [b] Crude product decomposition determined by LCMS and LC-UV analysis. [c] De determined by HPLC analysis of crude product of TFA cleavage of 20-50 mg portion of resin after benzylation reaction. [d] Side-chain cleavage reaction employed LiOOH as the nucleophile. [e] Isolated yield after appropriate work-up, based upon calculated loading of N-H oxazolidin-2-one* **1** *onto 2-Cl-Trt resin with yield quoted over three steps – N-acylation, enolate alkylation and side-chain cleavage. [f] Ee determined by HPLC analysis of side-chain cleaved product after appropriate work-up. [g] Reaction conducted as before but resin sealed within an IRORI mini-Kan™ in 10 mL dry THF.*

iv) Increasing the excess of reagents...

As increasing the reaction duration appeared to give inferior yields, an alternative method of driving the enolate alkylation reaction to completion was attempted. One of the frequently quoted advantages of using solid phase chemistry for synthesis is the opportunity to use a large excess of reagents to drive a reaction to completion using excess reagents that are removed by simple filtration of the polymer supported products. Hence, following a slight variation of the method of Burgess, *N*-propionyl oxazolidin-2-one resin **145** was treated with 10 equivalents of LHMDS at -15 °C for 30 min. before addition of 20 equivalents of benzyl bromide and subsequent stirring at the same temperature for a further 50 minutes (see Table 4.3b, entry 2). As seen previously for short duration reactions at -15 °C, there was still a significant amount of unreacted *N*-propionyl oxazolidin-2-one **144**

remaining (15%), indicating that despite the large excess of reagents, the reaction had once again not proceeded to completion. Despite this, the diastereoselectivity of the reaction was very high, with a de of 90% (85% ee after LiOOH cleavage). Also pleasingly the levels of *N*-H oxazolidin-2-one **1** and *N*-benzyl-oxazolidin-2-one **149** arising from these conditions were greatly decreased.

v) Increasing the reaction duration...

Repetition of these reaction conditions for a longer duration (12 hours) (see table 4.3b, entry 3) resulted in complete consumption of all the *N*-propionyl starting material **144**, but did not result in increased levels of α-benzylated product **149** being produced with a dramatic decrease in the observed levels of diastereoselectivity (68% de). It should be noted that for this reaction (and subsequent ones) the enolate alkylation reaction procedure needed to be altered. Previously, the *N*-propionyl oxazolidin-2-one functionalised polymer had been reacted by stirring loose resin in a 25 mL flask using a magnetic flea. For short duration experiments this was acceptable, however excessive magnetic stirring of cross-linked polystyrene resins was not advisable for prolonged periods because it resulted in 'grinding' of the resin beads.

vi) The use of Irori Kans™

In order to protect the resin beads, during these prolonged duration experiments, IRORI mini-Kan™ reactors were used for synthesis. IRORI Kan™ microreactors are a family of small polypropylene capsules with polypropylene mesh side walls and cap. The resin is placed inside the Kan whose mesh walls are designed to encapsulate the resin yet still allow solvated reagents to enter and react with the resin-bound reagents in a normal manner. In this way the resin is kept away from the magnetic stirrer bar and hence normal laboratory glassware and magnetic stirring facilities can be used (see Fig 4.3a). These Kans were originally designed to be used with a radiofrequency 'tag' encased within them however in this work the reactions were conducted individually and therefore this means of

identification was not required. It should be noted that in order to fully submerge the resin-filled Kan it was necessary to use an additional 4 ml of THF as solvent (10 ml in total). Therefore, the concentration of LHMDS in the reactions involving 10 equivalents LHMDS using IRORI Kan™ technology was actually only twice that of the reactions employing 3 equivalents of LHMDS conducted previously with 'loose' resin in 6 mL of THF.

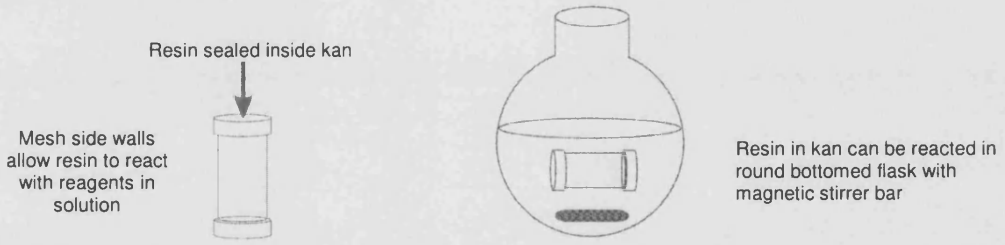


Fig 4.3a: Structure of IRORI kan ™ reactor and its use with magnetic stirring equipment.

From the above experiments it was noted that a significant amount of *N*-H oxazolidin-2-one **1** was being formed, presumably from enolate decomposition, and as a consequence concerns were raised over the conditions used to quench the reaction. Previously, solid phase enolate alkylations had been quenched by addition of 2 mL saturated ammonium chloride solution with no fixed time period observed between the quench and filtration of the resin. It was proposed that the addition of water to excess LHMDS present at the end of the alkylation reaction might produce LiOH that could inadvertently result in nucleophilic side chain cleavage on prolonged contact with the resin. Although never observed in solution phase, there was a possibility that this might explain the greater than expected amount of *N*-H oxazolidin-2-one auxiliary **1** being observed in our polymer-supported enolate alkylation reactions. It was therefore decided to quench all subsequent enolate alkylation reactions with 0.16 M pH 7 phosphate buffer to limit the effects of any LiOH formed and also to filter, wash and dry the alkylated resin immediately after quenching. However, repetition of some of the experiments described above, employing this new quench method did not result in any significant alteration in either the crude product composition, or the diastereoselectivity observed.

At this stage, it became apparent that extensive reaction optimisation would be required to develop optimal reaction conditions for solid supported asymmetric enolate alkylation

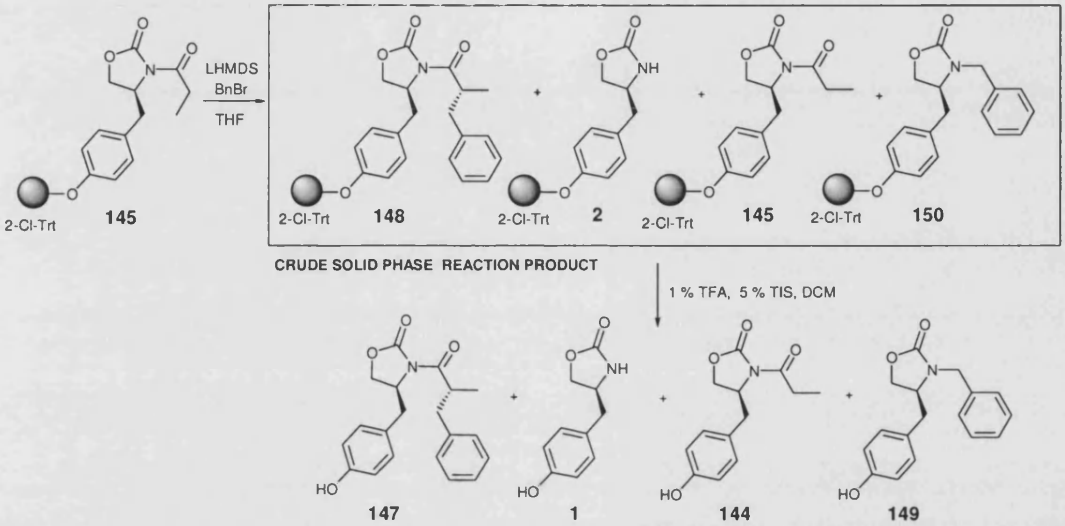
reactions. The results already gained had demonstrated a good correlation between the measurements of the de of **147** and ee of **(*R*)-65**, so it was concluded that it was no longer necessary to perform both measurements. Therefore, the stereoselectivity of all subsequent enolate alkylation optimisation reactions was determined using TFA cleavage of a small portion of resin enabling the de of **147** to be determined in the usual manner.

vii) Changing the order of reagent addition...

To further explore the unwanted occurrence of enolate decomposition on polymer support, the effect of changing the order of addition of reagents was investigated. In all the reactions previously described, the enolate had been preformed before addition of the electrophile (benzyl bromide) since this was the procedure favoured for solution phase enolate alkylations. This order is generally employed to avoid prolonged contact between the base and electrophile as some electrophiles can undergo unwanted elimination reactions under strongly basic conditions. However, this method relies on the enolate being sufficiently stable to survive the 'deprotonation' period before addition of the electrophile. Although this was the case in the solution phase enolate alkylation reactions of *N*-acyl-oxazolidin-2-ones previously investigated, it was not necessarily the case on solid phase since it was possible that the solid-supported enolate was decomposing before addition of the electrophile. It was therefore reasoned that formation of the enolate in the presence of the electrophile might be beneficial since the electrophile would be present to intercept the enolate the instant it was formed, thus hopefully preventing the competing enolate decomposition pathway. As benzyl bromide is not a base-sensitive electrophile the model transformation could be conducted in this manner without any concerns regarding reagent compatibility.

Oxazolidin-2-one functionalized resin **145** (in an IRORI mini-Kan™) in a solution of THF and 20 equivalents of benzyl bromide was treated with 10 equivalents of LHMDS at -15 °C followed by stirring for 12 hours (see Table 4.3c., entries 1 and 2). However, there was no sign of any reduction in the occurrence of enolate decomposition as demonstrated by *N*-H

oxazolidin-2-one **1** comprising around 40% of the crude product mixture. Furthermore there was no significant change in the diastereoselectivity of **147** suggesting there is no significant difference between pre-formation of the enolate and generating the enolate in the presence of the electrophile.



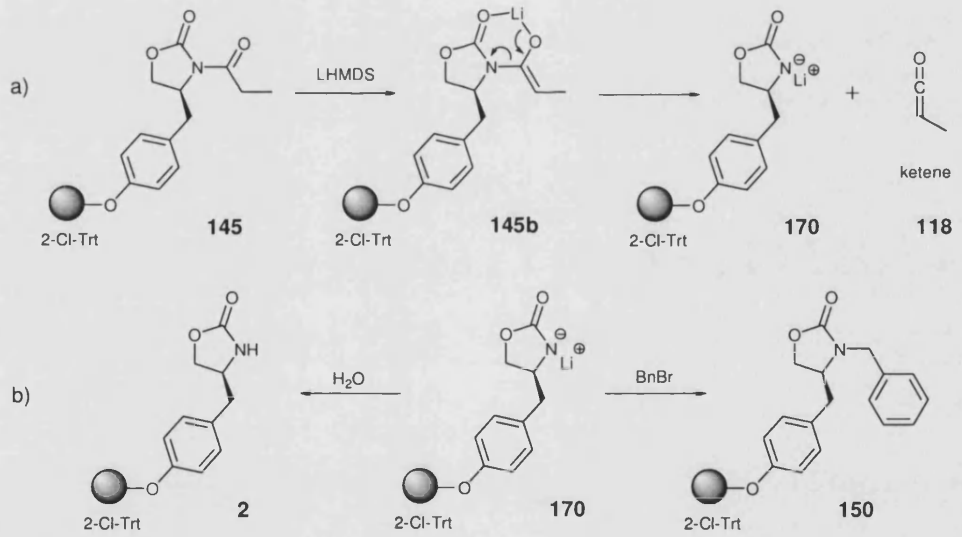
Scheme 4.3f: *Solid phase enolate alkylation of 150 mg of solid-supported N-propionyl oxazolidin-2-one* **145**, *with subsequent cleavage of a 20 mg portion of resin with 1% TFA and 5% TIS in DCM to give crude reaction products which were analysed via LC/UV and HPLC analysis to determine product composition and de respectively.*

Entry	Reaction conditions [a]		Composition of crude product from TFA cleavage (%) [b]				De of **147** [c] (%)
	Equiv. LHMDS	Reaction duration	α-benzyl **147**	*N*-H **1**	*N*-prop **144**	*N*-benzyl **149**	
1	10	20 equiv. BnBr first, then LHMDS 12 h	50	43	0	7	68
2	10	20 equiv. BnBr first, then LHMDS 12 h	58	42	0	0	76

Table 4.3c: [a] *Reaction conducted as follows: 10 equiv. LHMDS added to 150 mg pre-swollen resin* **145** *in IRORI mini-Kan™ in solution of 20 equiv. BnBr and 10 mL dry THF at -15 °C. Reaction stirred for 12 hours at -15 °C then quenched.* [b] *Crude product decomposition determined by LCMS and LC-UV analysis.* [c] *De determined by HPLC analysis of crude product following TFA cleavage of 20-50 mg portion of resin after alkylation reaction.*

viii) Investigating enolate decomposition and N-benzyl formation.

However, whilst these experiments (and those previously discussed) revealed that enolate decomposition is prevalent in these polymer-supported enolate alkylation reactions, the amount of *N*-benzyl auxiliary **149** formed was always significantly smaller than the amount of *N*-H oxazolidin-2-one **1** and rarely comprised more than 7% of the crude product mixture. Consideration of the proposed mechanism for decomposition of enolates of *N*-acyl-oxazolidin-2-ones (see Scheme 4.3g) reveals that removal of the side chain fragment is proposed to occur *via* loss of ketene **118** to afford an oxazolidin-2-one fragment with an anionic nitrogen atom. The lithiated anion of the parent oxazolidin-2-one **170** is then free to react with excess benzyl bromide to form the *N*-benzyl species **150**, or it may react with a proton source (presumably upon aqueous quenching of the alkylation reaction) to form the parent *N*-H oxazolidin-2-one **2**.



Scheme 4.3g: *a) Formation and decomposition of enolate of N-propionyl oxazolidin-2-one to afford N-lithiated oxazolidin-2-one* **170** *and ketene* **118**. *b) Quenching of N-lithiated oxazolidin-2-one* **170** *with BnBr to form N-benzyl-oxazolidin-2-one* **150** *or protonation to afford N-H-oxazolidin-2-one* **2**.

Under the reaction conditions investigated so far, there had always been an excess of benzyl bromide present. Therefore, it appears that the *N*-lithiated oxazolidin-2-one **170** does not react readily with benzyl bromide under these conditions and persists unreacted

until quenched by water at the end of the alkylation reaction. This suggests that **170** is relatively stable at low temperatures and hence alkylation with benzyl bromide is slow. A review of the literature supports this observation since *N*-benzylation of lithium anions of oxazolidin-2-ones generally requires reaction at room temperature. [83,84]

This feature is advantageous for the potential recycling of the solid-supported chiral auxiliary. As discussed earlier, whilst the formation of *N*-H oxazolidin-2-one **2** in the enolate alkylation reaction is clearly not desirable as it reduces the yield of alkylated product, it is not disastrous as it does no permanent damage to the auxiliary fragment which can simply be re-acylated and reused in the resin's next cycle. However, formation of the *N*-benzyl oxazolidin-2-one **150** results in irreversible alkylation of the polymer supported oxazolidin-2-one fragment which results not only in a decrease in the yield of α-benzylated product **148** in the current reaction cycle, but also a decrease in the amount of chiral auxiliary available for subsequent reactions using that batch of resin. As the ultimate aim of this study was to create a reusable solid-supported chiral auxiliary, significant levels of *N*-benzyl formation would be highly detrimental to the system's success. Therefore, the observation that *N*-benzyl-oxazolidin-2-one **150** formation is slow, even with a large excess of benzyl bromide was highly encouraging.

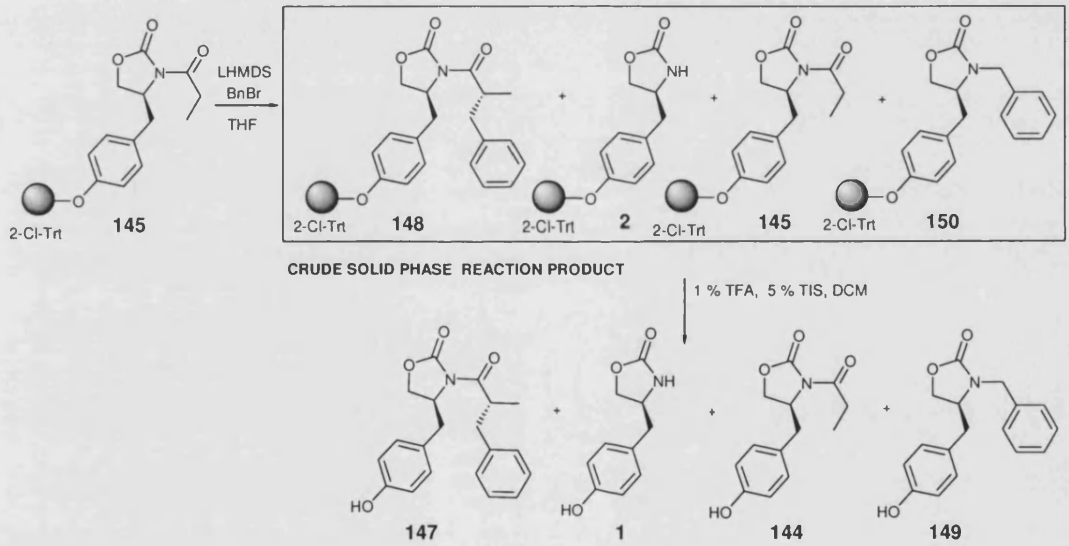
ix) Summary to date...

Considering all the results discussed above, the following conclusions were drawn.

1) Enolate decomposition is occurring extensively, even at -15 °C over short durations, resulting in significant amounts of *N*-H oxazolidin-2-one **2**. Fortunately *N*-benzylation of the lithium anion of **2** is slow therefore only a small amount of *N*-benzyl-oxazolidin-2-one is formed even when extensive enolate decomposition occurs.
2) Both the yield and de of the alkylated product appear to diminish with time.
3) The use of large excesses of reagents appears to consume all of the *N*-propionyl oxazolidin-2-one **145** starting material, and encourage the alkylation reaction to proceed to completion.

x) Multiple treatments with reagents

The next strategy investigated aimed to use multiple treatments involving sequential treatments with LHMDS and BnBr, in the hope that all the starting material would be reacted over a series of short reaction times. This strategy had been reported to have been employed successfully for solid-supported oxazolidin-2-one mediated aldol reactions.[32] Hence, *N*-propionyl resin **145** in an IRORI kan™ was treated with 10 equivalents of LHMDS for 30 minutes at -15 °C before addition of 20 equivalents of benzyl bromide, and the reaction stirred for a further 60 minutes. The reaction solution was then removed from the reaction vessel *via* cannula, the resin re-suspended in fresh, pre-chilled THF and the deprotonation / alkylation process repeated two further times.



Scheme 4.3h: *Solid phase enolate alkylation of 150 mg of solid-supported N-propionyl oxazolidin-2-one* **145**, *with subsequent cleavage of a 20 mg portion of resin with 1% TFA and 5% TIS in DCM to give crude reaction products which were analysed via LC/UV and HPLC analysis to determine product composition and de respectively.*

Entry	Reaction conditions [a]		Composition of crude product from TFA cleavage (%) [b]				de of **147** [c] (%)
	Equiv. LHMDS	Reaction duration	α-benzyl **147**	*N*-H **1**	*N*-prop **144**	*N*-benzyl **149**	
1	10	LHMDS, 30 min. then BnBr, 60 min. (3 x treatment)	63	25	7	5	81
2	10	LHMDS, 30 min. then BnBr, 60 min. (3 x treatment)	22	59	13	7	78

Table 4.3d: **Investigating effect of multiple treatments of resin with reagents.**
[a] *Reaction conducted as follows: 10 equiv. LHMDS added to 150 mg pre-swollen resin* **145** *in IRORI mini-Kan™ in 10 mL dry THF at -15 °C. Reaction stirred for 30 minutes before addition of BnBr followed by stirring for 60 minutes at -15 °C. Reaction solution then removed from vessel via cannula and resin resuspended in 10 mL fresh, dry THF that had been pre-chilled to -15 °C. Reaction cycle repeated a further 2 times.* [b] *Crude product decomposition determined by LCMS and LC-UV analysis.* [c] *de determined by HPLC analysis of crude product of TFA cleavage of 20-50 mg portion of resin after alkylation reaction.*

Initially these modified conditions appeared relatively successful with 63% of the crude product being the desired α-benzylated product **147** with a relatively good de (81%) (see Table 4.3d, entry 1). There was still a significant amount of *N*-H oxazolidin-2-one **1** present (25%) but only trace amounts of the undesired *N*-benzyl **149** and *N*-propionyl **144** auxiliaries. However, upon repetition of this reaction (see Table 4.3d, entry 2), dramatically different product composition results were achieved, with a very poor conversion to α-benzylated product (22%) and extensive enolate decomposition. Further repetitions of this experiment revealed that although these conditions were capable of producing good results, it was very capricious, presumably due to the high level of physical manipulation involved over the three cycles of this protocol. This afforded many opportunities for contamination of the reaction which was already known to be temperature and moisture sensitive. So, although with care this procedure might prove to be effective, a simpler experimental procedure was clearly desirable.

xi) Epimerisation of the N-alkylated product?

These results again suggested that short reaction durations were required to ensure high levels of diastereoselectivity as the de of the alkylated product appeared to decrease with

time. This trend was also briefly commented on by Burgess *et al.*[25] but no reference was made to the relevant time-scale or any explanation offered for this loss of stereocontrol. As the de of the α-benzylated product **147** is high after a short duration, the enolate alkylation reaction must be proceeding with high diastereoselectivity. This suggests that the decrease in de of the α-benzylated product **147** that occurred over longer durations might be due to epimerisation of the newly formed chiral centre of the benzylated product **148** rather than poor diastereoselectivity in the initial enolate benzylation reaction. It would therefore appear that the excess base used to effect enolate formation was also causing epimerisation of the α-benzylated product over time. Under normal solution phase conditions, it is reported that α-alkylated products are stable to the presence of excess base remaining after enolate formation. This is because the α-alkylated oxazolidin-2-one has to adopt a conformation that positions its α-proton orthogonal to the exocyclic carbonyl group for enolate formation to occur, as depicted in Fig. 4.3b. Whilst conformers B and C meet the stereoelectronic requirement for enolisation to occur, they are much higher in energy than conformer A due to 1,3-allylic strain interactions between the oxazolidin-2-one fragments and R_1 and R_2 substituents of the acyl fragment. Therefore, the energetically more favourable conformer A predominates in solution, and as a consequence enolisation does not occur and the α-stereocentre is stable under basic conditions.

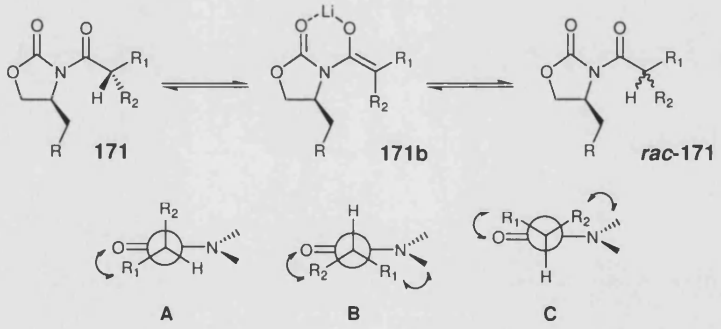


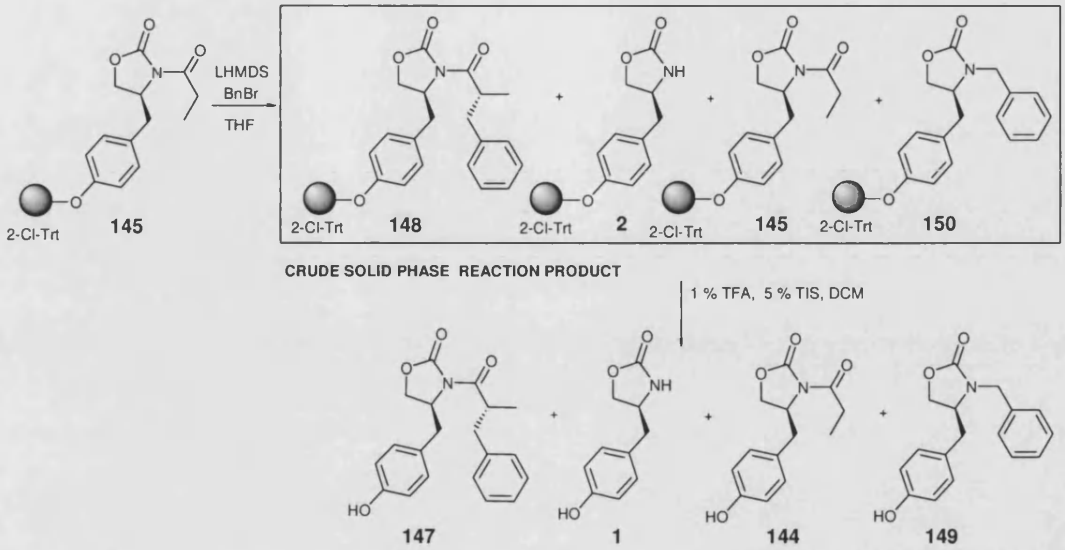
Fig. 4.3b: *Epimerisation via enolisation of the α-stereocentre of* **171** *is unlikely to occur due to allylic strain. Conformers B and C meet the stereoelectronic requirement for enolisation but are higher in energy than conformer A which disfavours enolisation.*

A comprehensive review of the literature could find no reports on epimerisation of α-alkylated *N*-acyl-oxazolidin-2-ones by excess base present in enolate alkylation reactions. However, most solution phase reactions of this type only employ a small excess of base (typically 1.1 to 1.5 equivalents) and it is possible that the large excess of base (3 or 10

equivalents) used to drive my solid phase alkylation reaction to completion, could also result in epimerisation occurring despite unfavourable interactions caused by allylic strain.

If this theory was correct, and the excess of base was indeed causing epimerisation of the α-benzylated product on solid phase, then it was reasoned that a simple alteration to the reaction protocol should eliminate this problem. Therefore it was reasoned that simply removing excess base from the reaction vessel *after* formation of the solid-supported enolate, but *before* addition of the electrophile, would prevent the excess base from ever being in contact with the α-benzylated product **148**. If successful, this would still allow a large excess of reagents to be used to drive the reaction to completion but would eliminate the epimerisation problem.

N-Propionyl oxazolidin-2-one resin **145** encased in an IRORI mini-kan™ was therefore treated with 10 equivalents of LHMDS at -15 °C for 2 hours. After this time, the reaction solvent containing the excess base that surrounded the Kan was removed *via* cannula. The resin was then resuspended in fresh, dry THF pre-chilled to -15 °C and treated with 20 equivalents of benzyl bromide for 12 hours. Gratifyingly, the de of the α-benzylated product **147** was high (89% de) (see Table 4.3e, entry 1) and comparison of this result with those obtained in control reactions under similar conditions, but without removal of the excess base (see Table 4.3e, entries 2 and 3), demonstrated that removal of the excess base before addition of the electrophile was indeed beneficial.



Scheme 4.3j: *Solid phase enolate alkylation of 150 mg of solid-supported N-propionyl oxazolidin-2-one* **145**, *with subsequent cleavage of a 20 mg portion of resin with 1% TFA and 5% TIS in DCM to give crude reaction products which were analysed via LC/UV and HPLC analysis to determine product composition and de respectively.*

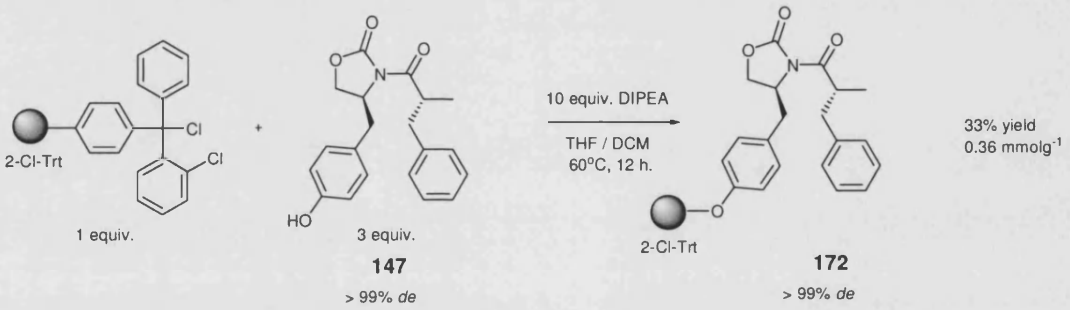
Entry	Reaction conditions [a]		Composition of crude product after TFA cleavage (%) [b]				De of **147** [c] (%)
	Equiv. LHMDS	Reaction duration	α-benzyl **147**	*N*-H **1**	*N*-prop **144**	*N*-benzyl **149**	
1	10	LHMDS, 2 h, drain then BnBr, 12 h.	65	26	3	6	89
2	10	LHMDS, 2h. then BnBr, 12 h.	55	38	0	7	74
3	10	BnBr, then LHMDS, 12 h.	50	43	0	7	68

Table 4.3e: ***Investigating the order the addition of reagents and the effect of removing excess base from the reaction solution before addition of the electrophile***

[a] *Reaction conducted as follows: 10 equiv. LHMDS added to 150 mg pre-swollen resin* **145** *in IRORI mini-Kan™ in 10 mL dry THF at -15 °C. Reaction stirred for stated period of time before removal of reaction solution via cannula. Resin resuspended in 10 mL fresh, dry THF that had been pre-chilled to -15 °C, BnBr added and reaction stirred for a further time period as stated.* [b] *Crude product decomposition determined by LCMS and LC-UV analysis.* [c] *De determined by HPLC analysis of crude product of TFA cleavage of 20-50 mg portion of resin after alkylation reaction.*

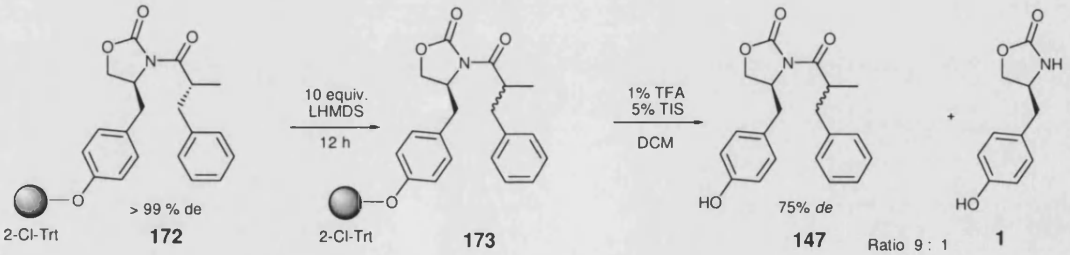
To confirm that the decrease in the de of the alkylated product with time was indeed due to epimerisation of the newly formed chiral centre of **148** by excess LHMDS, a control experiment was conducted. Diastereomerically pure (>99% de) *N*-alkylated oxazolidin-2-one fragment **147** that had been prepared in solution phase was immobilised onto 2-chlorotrityl chloride resin under standard conditions, albeit in a poor 33% yield (Scheme

4.3k). Collection and evaporation of the washings after filtration of the resin yielded impure α-benzyl-**147** contaminated with DIPEA, which after washing with 1.0 M HCl (aq) afforded pure α-benzyl-**147**. ^{1}H-NMR and HPLC analysis of **147** confirmed a >99% de, showing that the α-benzylated fragment had not been epimerised under the immobilisation conditions. Additionally, in order to calculate the loading and to again confirm that no epimerisation had occurred upon immobilisation, a portion of resin **172** was cleaved *via* treatment with 1% TFA and 5% TIS in DCM, which once again afforded **147** in >99% de.



Scheme 4.3k: *Immobilisation of α-benzylated oxazolidin-2-one* **147** *onto 2-chlorotrityl chloride resin.*

This diasteromerically pure functionalised resin **172** (in an IRORI mini-kan™) was then treated with 10 equivalents of LHMDS at -15 °C in THF for 12 hours, under analogous conditions to those of the extended enolate alkylation reactions (see Scheme 4.3m). The resin **173** was then cleaved (1% TFA, 5% TIS, DCM) to afford diastereomeric product **147**, which HPLC analysis revealed a de of 75%. This reaction therefore confirms that excess base causes epimerisation of the newly formed chiral centre of the alkylated product on polymer support.



Scheme 4.3m: *Treatment of functionalised resin* **172** *with 10 equivalents LHMDS at -15 °C for 12 hours and subsequent TFA cleavage of resulting resin* **173** *demonstrates that enolisation of alkylated product* **172** *results in both epimerisation of* **147** *and enolate decomposition to N-H oxazolidin-2-one* **1**.

In addition to the partially epimerised α-benzylated product **147**, some *N*-H oxazolidin-2-one **1** was observed. Again, this indicates that enolisation of the alkylated product has occurred, with a small proportion of the enolate decomposing to its parent oxazolidin-2-one (see Fig 4.3c).

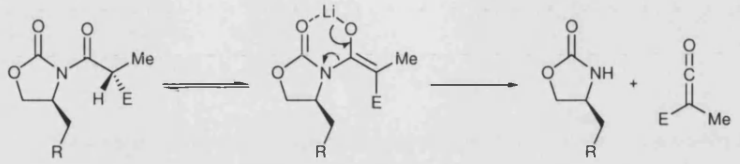
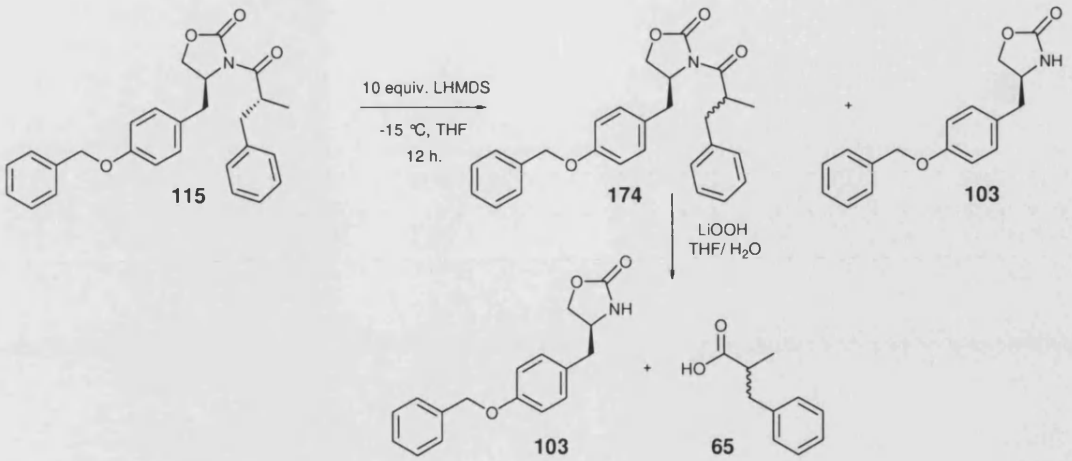


Fig. 4.3c: *Mechanism of enolisation of alkylated product by excess LHMDS with subsequent enolate decomposition and formation of N-H oxazolidin-2-one and ketene.*

xii) Solution phase enolate epimerisation and decomposition studies...

To investigate the epimerisation reaction further and to confirm that its occurrence was not purely associated with the solid phase nature of the enolate alkylation reactions studied herein, solution phase time-course studies were then conducted.

Hence diasteromerically pure α-benzyl-oxazolidin-2-one **115** was treated with 10 equivalents of LHMDS in THF at -15 °C over a period of 12 hours (see Scheme 4.3n) and aliquots of the reaction mixture taken at regular intervals and quenched with pH7 phosphate buffer. ^{1}H-NMR analysis of the crude reaction product allowed the relative amounts of epimerised-*N*-alkylated product **174** and *N*-H oxazolidin-2-one **103** to be determined. The crude reaction product was then cleaved with LiOOH (generated *in situ* from H_2O_2 and LiOH) in THF / H_2O solution. The crude product, consisting of both *N*-H oxazolidin-2-one **103** and 2-benzylpropanoic acid **65** was then analysed by chiral HPLC and the *ee* of **65** determined.



Scheme 4.3n: *Solution phase decomposition studies: Diasteromerically pure oxazolidin-2-one* **115** *was treated with 10 equiv. LHMDS at -15 °C in 8 mL dry THF for 12 hours with the crude product composition of aliquots sampled over time determined by* ^{1}*H-NMR spectroscopy. Crude reaction product then cleaved using LiOOH and the ee of the resulting 2-benzylpropanoic acid* **65** *determined by HPLC.*

Time (min.)	ee of acid (%) [a]	α-benzylated oxazolidin-2-one **174** remaining (%) [b]	*N*-H-oxazolidin-2-one **103** formed (%)
0	100	100	0
15	93	83	17
30	90	82	18
60	81	82	18
120	74	78	22
240	65	78	22
480	62	74	26

Table 4.3f: *Solution phase decomposition studies. Diastereomerically pure α-benzyl-oxazolidin-2-one* **115** *treated with 10 equiv. LHMDS and subsequent epimerisation / enolate decomposition monitored.* [a] *Ee of acid determined by HPLC.* [b] *Percentage of crude product as determined by* ^{1}*H-NMR.*

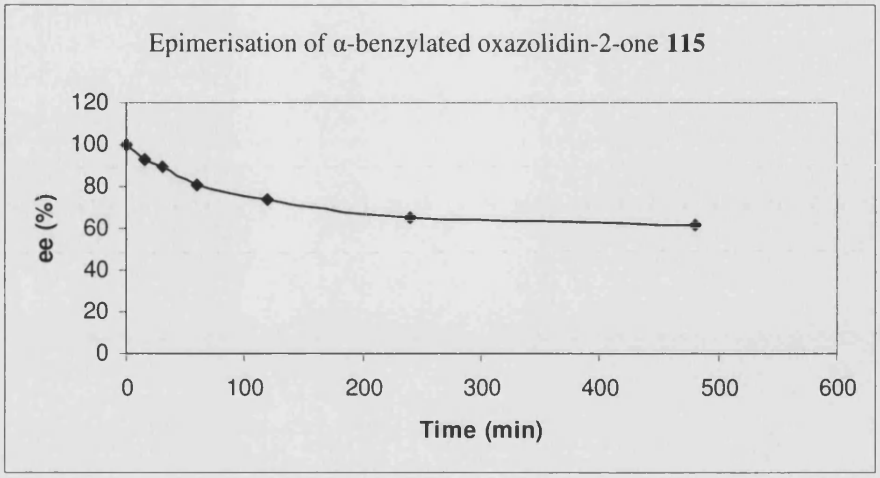


Fig 4.3d: *Graph to show epimerisation of α-benzylated-***115** *with time upon treatment with 10 equivalents of LHMDS at -15 °C, as demonstrated by determination of the ee of 2-benzyl-propionic acid* **65** *recovered after LiOOH treatment of epimerised-α-benzylated-***174**.

These solution phase studies clearly demonstrate that the ee of the acid product formed was decreasing, indicating epimerisation of the newly formed stereogenic centre of α-benzyl-oxazolidin-2-one **174** over time (see Fig. 4.3d). It would appear that initially the rate of epimerisation (which is itself indicative of the rate of enolisation) is relatively fast, but that it decreases with time until a constant level is achieved. This implies an equilibrium is reached between the two diastereomers, in which the 'major' diastereomeric product of the enolate alkylation reaction is more thermodynamically favoured (see Fig. 4.3e).

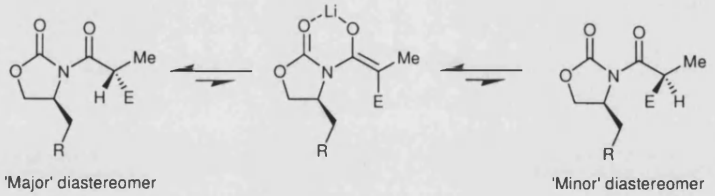


Fig 4.3e: *Epimerisation of the diastereomeric product of enolate alkylation favours the 'major' diastereomeric product as it minimises steric repulsion between the bulky R group and the electrophile.*

In an additional solution phase experiment, a 1:1 mixture of the two diastereomers **115** and **124** were treated with 10 equivalents of LHMDS for 12 hours at -15 °C, which upon work-up afforded a mixture of diastereomers with a de of 16% in favour of the major diastereomer.

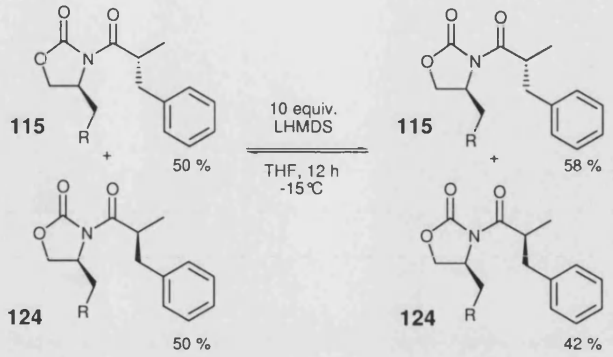


Fig 4.3f: *Epimerisation of a 1:1 mixture of diastereomers of α-alkylated oxazolidin-2-one results in a diastereoenriched product mixture.*

Any consideration of the de obtained in these epimerisation reactions must consider the fact that lithium enolates generally exist as aggregates. Lithium is usually tetra-coordinated, however it is reported that the degree of aggregation depends less upon the particular enolate structure than upon solvent and the presence of other complexing reagents.[85]

In the epimerisation reactions under consideration (see Scheme 4.3f), there are several different species capable of participating in a higher order aggregation state (see Fig 4.3g). It should also be noted that the enolate of the α-alkylated product is also prone to decomposition to afford the lithiated oxazolidin-2-one and ketene, further complicating the nature of the potential aggregation species.

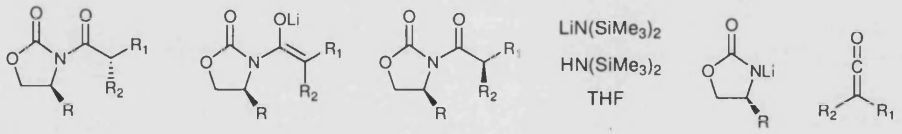
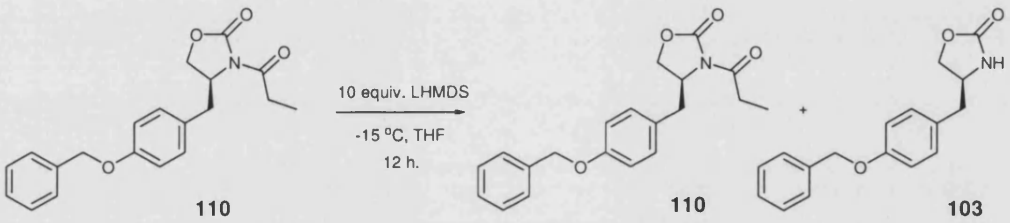


Fig 4.3g: *Species present in solution phase epimerisation of α-alkylated product reaction that could be involved in aggregation states.*

These species are capable of forming various pure and mixed aggregates, with the potential for each aggregate having a different reactivity / decomposition profile.[85] It is possible therefore that the ratio of products reached in the deprotonation (and hence epimerisation) of α-alkylated-oxazolidin-2-one is due to the formation of stable heterochiral aggregates corresponding to the ratio of diastereomers obtained. Furthermore, the formation of different 'mixed' aggregation states may account for the propensity of the α-alkylated

product to undergo deprotonation in the presence of an excess of LHMDS, yet remain configurationally stable with one equivalent of base.

This decomposition study therefore explains the observation that removal of the excess base before addition of the electrophile is beneficial to the solid-supported enolate alkylation reactions because it prevents enolisation of the α-benzylated product, consequently preventing epimerisation and enolate decomposition. However, the issue of *N*-propionyl enolate decomposition still remained and as a consequence, *N*-propionyl oxazolidin-2-one **110** was treated with 10 equivalents of LHMDS at -15 °C for 8 hours, with aliquots being removed at intervals and quenched (see Scheme 4.3p).



Scheme 4.3p: *Solution phase decomposition studies: N-propionyl oxazolidin-2-one* **110** *treated with 10 equiv. LHMDS and subsequent enolate decomposition to N-H oxazolidin-2-one monitored over time.*

Time (min)	*N*-propionyl oxazolidin-2-one **110** remaining (%)
0	100
15	72
30	72
60	69
120	71
240	70
480	71

Table 4.3g: *Solution phase decomposition studies. N-propionyl oxazolidin-2-one* **110** *treated with 10 equiv. LHMDS and subsequent enolate decomposition monitored by* ^{1}*H-NMR analysis.*

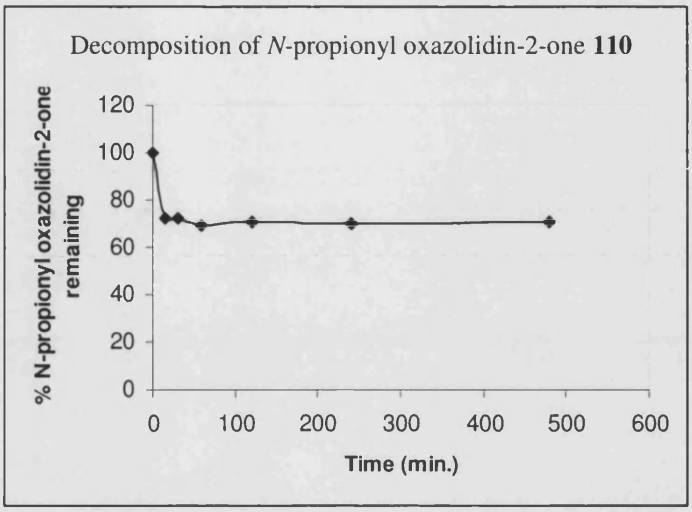


Fig. 4.3h: *Graph to show percentage of N-propionyl oxazolidin-2-one* **110** *remaining at a given time when N-propionyl oxazolidin-2-one is treated with 10 equivalents of LHMDS at -15 °C.*

Unsurprisingly, it was found that the enolate formed by deprotonation of the *N*-propionyl oxazolidin-2-one **110** by LHMDS was prone to decomposition (see Table 4.3g, Fig. 4.3h), with a trend being observed in which decomposition occurred very quickly in the initial stages of the reaction, then appeared to stabilise at around 75%. Again, this could be due to the formation of a stable aggregation state involving the anions of *N*-propionyl and *N*-H oxazolidin-2-ones in a 7:1 ratio, with other possible complexing species present being the eliminated ketene fragment and the secondary amine formed from protonation of LHMDS.

In both the solution phase enolisation reactions investigated in this section, aggregates of lithium enolates and other complexing reagents have been proposed to be directly involved in the reaction and reactivity and stereoselectivity of the lithium enolates of *N*-acyl-oxazolidin-2-one. However, the situation with solid phase lithium enolates is more complicated. It is often reported that immobilisation of a species onto a rigid, cross-linked polymer support results in reactive site isolation.[86] This approach has been proposed to be useful as an alternative to the solution phase 'high-dilution' effect for the synthesis of molecules prone to polymerisation. Conversely, it has also been demonstrated that site-site interactions on polymer support can occur to some extent Rapoport [87] and Scott [88] both demonstrating that the majority of functionalised sites on 1% and 2% DVB-crosslinked polystyrene can interact. It is therefore feasible that aggregation between polymer-

supported lithium enolates could be achieved. Regardless of site-site interactions, it is certainly possible for solid-supported enolates to form aggregated states with solution phase components, however it is possible that these interactions may not be identical to those formed in the corresponding solution phase system due to the presence of the polystyrene support. Overall, it must be concluded that proof of the nature of any higher-order, aggregated states in solution and solid phase reactions, cannot be made without a great deal of further experimentation and analysis in this area.

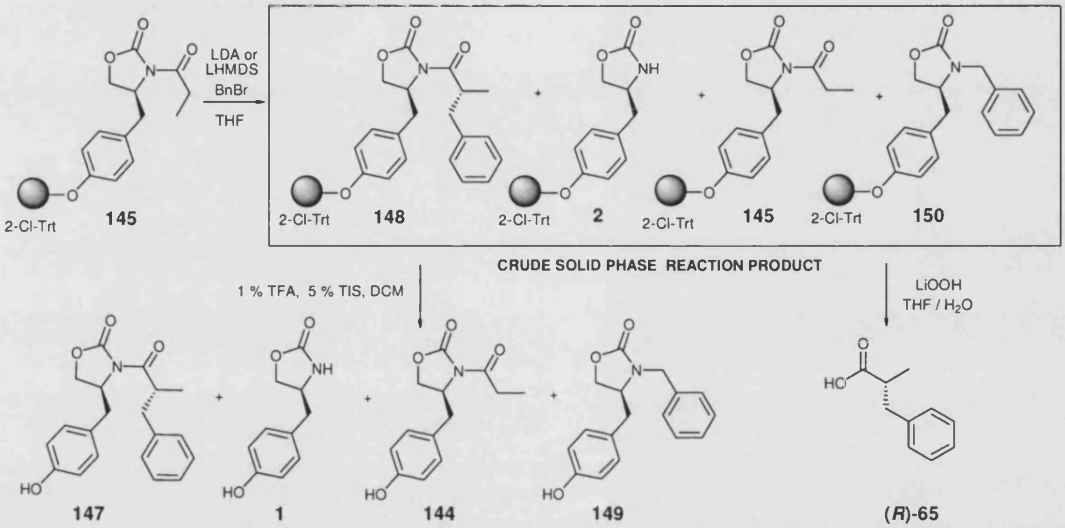
xiii) Bringing it all together...

In order to develop optimal reaction conditions for the model asymmetric enolate alkylation reaction, it was necessary to reconsider the information discovered in these studies.
The key observations were

1) Both the yield and de of the alkylated product diminished with time due to enolisation of the alkylated product by the excess LHMDS present. However, both issues could be avoided by removal of the excess LHMDS solution from the resin after enolate formation before addition of the electrophile.
2) Partial decomposition of the enolate of the *N*-propionyl oxazolidin-2-one appears inevitable due to the large excesses of base required for efficient enolate formation, even at -15 °C over short durations

Following on from the previous optimisation reaction investigating the effect of removal of the excess base (see Table 4.3h, entry 1), it was found that a 65% yield of α-benzylated product **147** could be achieved with a de of 89% when the polymer-supported *N*-acyl-oxazolidin-2-one **145** was treated for 2 hours with LHMDS which was then drained followed by a 12 hour reaction of the enolate with benzyl bromide. However, this resulted in 26% *N*-H oxazolidin-2-one **1** being formed by enolate decomposition and it was reasoned that this might be further reduced by decreasing the duration of the enolate formation step. Indeed decreasing the enolate formation period to 30 minutes and decreasing the total reaction duration to a total of 80 minutes (Table 4.3h, entry 2), did result in a slight decrease in the amount of *N*-H oxazolidin-2-one **1** formed, although it also

resulted in some starting material *N*-propionyl oxazolidin-2-one **144** remaining. This result was very encouraging as the yield and de of the alkylated product were high (63% and 95% respectively). To confirm these values, LiOOH side chain cleavage was also conducted and 2-benzylpropionic acid **(*R*)-65** isolated in good yield (59%) and excellent ee (96%).



Scheme 4.3q: *Solid phase enolate alkylation of 150 mg of solid-supported N-propionyl oxazolidin-2-one* **145**, *with subsequent cleavage of a 20 mg portion of resin with 1% TFA and 5% TIS in DCM to give crude reaction products which were analysed via LC/UV and HPLC analysis to determine product composition and de respectively. Remaining 120 mg alkylated resin treated with LiOOH to give acid* **(*R*)-65**, *with the ee of chiral products being determined by chiral HPLC.*

Entry	Reaction conditions [a]		Composition of crude product from TFA cleavage (%) [b]				De of **147** [c] (%)	Yield [d] and ee[e] of acid **(*R*)-65**
	Equiv. LHMDS	Reaction duration	α-benzyl **147**	*N*-H **1**	*N*-prop **144**	*N*-benzyl **149**		
1	10	LHMDS, 2 h at -15 °C, drain, then BnBr for 12 h at -15 °C.	65	26	3	6	89	Not cleaved
2	10	LHMDS, 30 min at -15 °C, drain, then BnBr for 30 min at -15 °C, then 20 min warming from -15 °C to rt	63	20	14	3	95	59% yield (96% ee)
3	10	LHMDS, 30 min at 0 °C, drain then BnBr for 5 min at 0 °C, then 20 min warming from 0 °C to rt.	77	20	0	2	96	69% yield (95% ee)
4	3	LHMDS, 30 min at 0 °C, drain then BnBr for 5 min at 0 °C, then 20 min warming from 0 °C to rt	70	24	2	3	95	63% yield (97% ee)

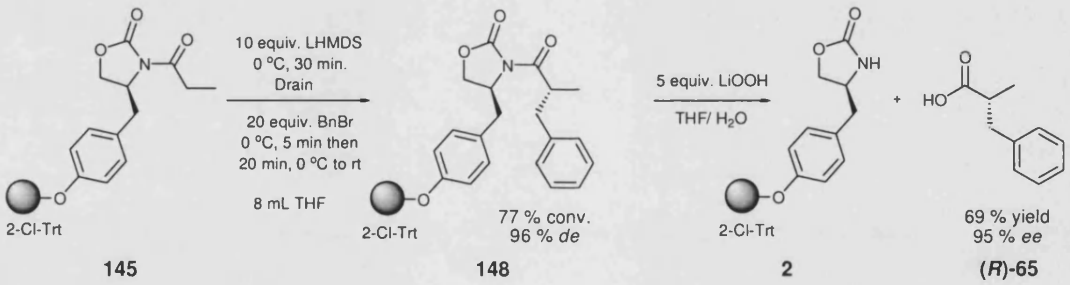
Table 4.3h: ***Investigating the effect of removing the excess of base, raising the temperature and decreasing the reaction duration.***

[a] Reaction conducted as follows: 10 equiv. of LHMDS was added to 150 mg pre-swollen resin **145** *sealed into IRORI mini-kan™ in 8 mL dry THF at stated temperature and stirred for the stated amount of time before removal of the reaction solution via cannula. The resin was resuspended in 8 mL fresh, dry THF and BnBr added (when 3 equiv. of LHMDS used then 5 equiv. of BnBr used, when 10 equiv. of LHMDS used then 20 equiv. of BnBr used). Reaction stirred for a further stated period of time at stated temperature then quenched. [b] Crude product decomposition determined by LCMS and LC-UV analysis. [c] De determined by HPLC analysis of crude product of TFA cleavage of 20-50 mg portion of resin after alkylation reaction. [d] Isolated yield after appropriate work-up, based upon the calculated loading of N-H oxazolidin-2-one onto 2-Cl-Trt resin representing yield over three steps – N-acylation, enolate alkylation and side-chain cleavage. [e] Ee determined by HPLC analysis of side-chain cleaved product after appropriate work-up.*

In an effort to drive the enolate alkylation reaction to completion without extending the reaction time, the reaction was repeated at 0 °C rather than -15 °C (see Table 4.3h, entry 3). It was hoped that the elevated temperature, although likely to cause an increase in the rate of enolate decomposition, would also result in an increase in the rate of the desired alkylation reaction. Therefore, resin **145** was treated with 10 equivalents of LHMDS at 0 °C for 30 minutes, the solvent and excess base removed *via* cannula, and then 20 equivalents of BnBr added at 0 °C. The reaction was stirred for a further 5 minutes at 0 °C

and then allowed to warm to room temperature over a period of 20 minutes. Gratifyingly, excellent results were achieved with α-benzylated product **147** comprising a high 77% yield of the crude product of TFA cleavage and a very high de of 96% achieved. There was no evidence of a decreased diastereoselectivity due to the increase in temperature or an increase in the amount of *N*-benzyl oxazolidin-2-one **149** formed. Again LiOOH side-chain cleavage was conducted to afford 2-benzylpropionic acid **(*R*)-65** in 69% yield and 95% *ee*. In a final attempt to further improve the conditions, the excess of base (and hence the concentration) was reduced to establish whether this would result in less enolate decomposition at the elevated temperatures being used. However, repeating the previous reaction with 3 eq LHMDS gave results that were similar to those obtained when 10 equivalents of LHMDS were employed (see Table 4.3h, entry 4) but with a slightly lower yield of α-benzylated product **147** (70% of crude product mixture, corresponding to 63% isolated yield after LiOOH cleavage).

These results were now deemed satisfactory – α-benzylated product **147** could be prepared cleanly (see Fig. 4.3j) and in reasonable conversions considering the apparently inevitable decomposition of the enolate **145b** to *N*-H oxazolidin-2-one with excellent levels of diastereoselectivity (see Scheme 4.3r).



Scheme 4.3r: *Optimised reaction conditions developed for model transformation. 10 equivalents of LHMDS added to 150 mg N-propionyl resin* **145** *in IRORI mini-kan (resin preswollen in 8mL THF) at 0 °C and stirred at this temperature for 30 min. Reaction solution then removed via cannula and resin re-suspended in 8 mL fresh, pre-chilled THF. 20 equivalents of BnBr added and reaction stirred at 0 °C for 5 minutes, then removed from ice bath and allowed to stir for a further 20 mins.*

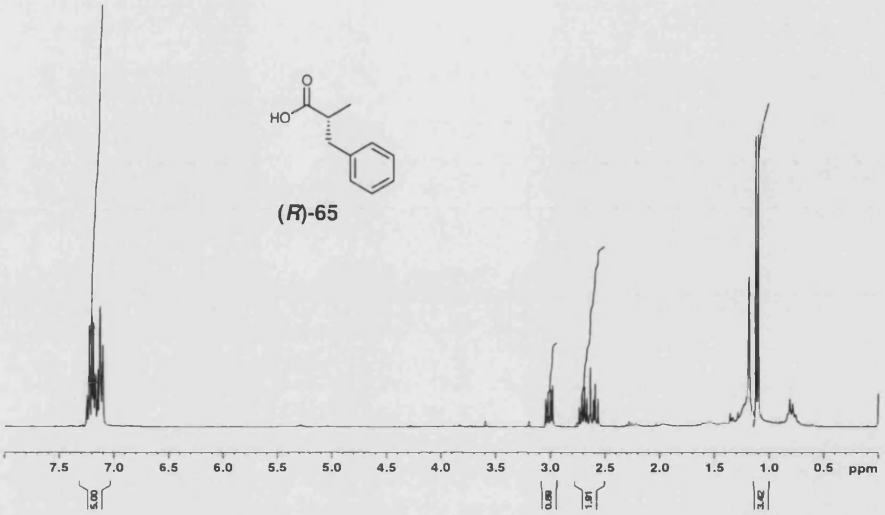


Fig 4.3j: *2-benzylpropionic acid* **(*R*)-65** *prepared via asymmetric enolate alkylation of solid supported N-propionyl-oxazolidin-2-one* **145** *with benzyl bromide, with subsequent cleavage of the acid product via LiOOH hydrolysis.*

4.4 Conclusions

To conclude, as depicted in Scheme 4.3r, reaction conditions had been developed that allowed an α-benzylated carboxylic acid to be prepared in acceptable yield and excellent *de*. It should be noted that although 10 equivalents of LHMDS and 20 equivalents of benzyl bromide were employed in these small scale reactions, only slightly reduced yields were gained using 3 equivalents of LHMDS and 5 equivalents of benzyl bromide. Therefore, if the use of such large excesses was undesirable, either due to safety concerns or reagent cost, the method could be easily adapted to use lower concentrations of reagents with relatively small losses in yield.

In developing these conditions, an understanding of the factors affecting solid-supported asymmetric enolate alkylation reactions was gained, including the conflicting temperature and time requirements for enolate reactivity versus enolate decomposition. It was found that enolate decomposition was inevitable if complete enolisation was to occur and hence quantitative yields of α-alkylated products were unlikely to be obtained. In addition the

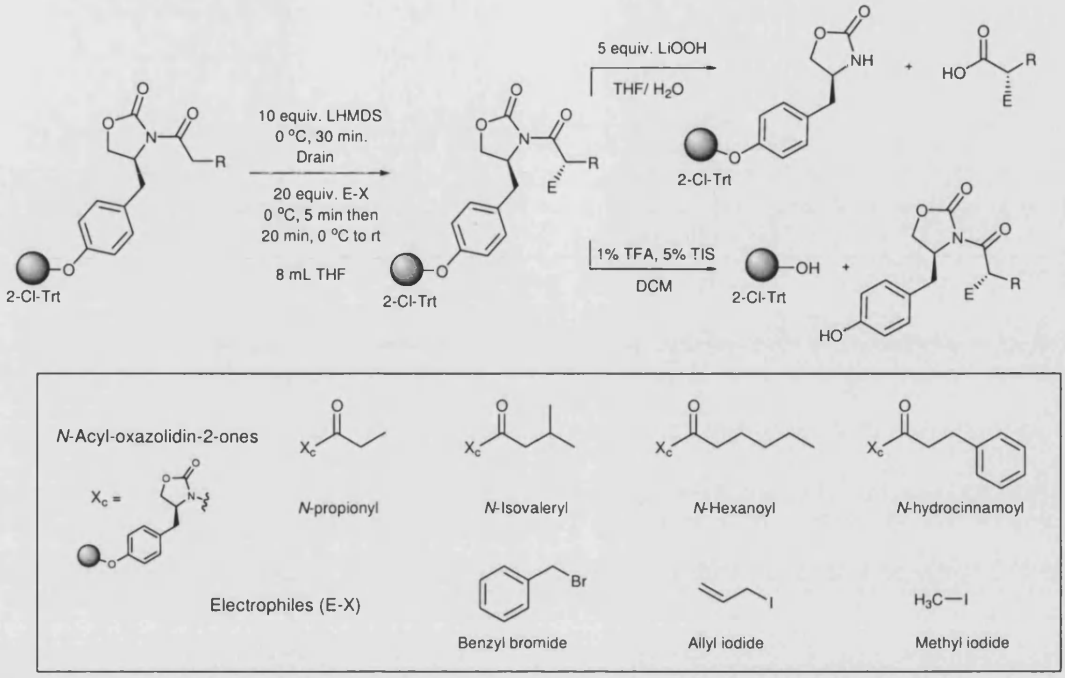
discovery was made that excess base can cause epimerisation of the newly formed chiral centre of the α-alkylated product.

Chapter 5: Application of solid-phase enolate alkylation reaction conditions to other systems

Overview

5.1 Alternative N-acyl-oxazolidin-2-ones and electrophiles

Having optimised reaction conditions for the asymmetric alkylation of the enolate of a polymer-supported *N*-propionyl oxazolidin-2-one **145** with benzyl bromide (see Scheme 4.3r), it was necessary to determine whether these conditions could be applied successfully to other types of polymer-supported *N*-acyl-oxazolidin-2-ones and electrophiles.

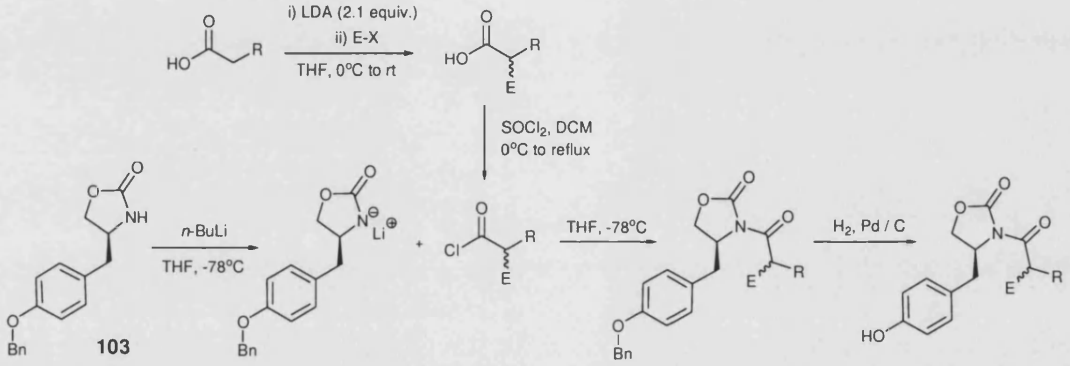


Scheme 5.1a: *Proposed array of enolate alkylation reactions to be conducted according to the previously optimised protocol (see Section 4.3)*

The proposed array (depicted in Scheme 5.1a) was comprised of four different *N*-acyl oxazolidin-2-ones (*N*-propionyl, *N*-isovaleryl, *N*-hexanoyl and *N*-hydrocinnamoyl) and three different electrophiles (benzyl bromide, allyl iodide and methyl iodide). This selection of reactive components aimed to explore the scope and limitation of the solid supported asymmetric enolate alkylation reaction conditions developed for the model reaction.

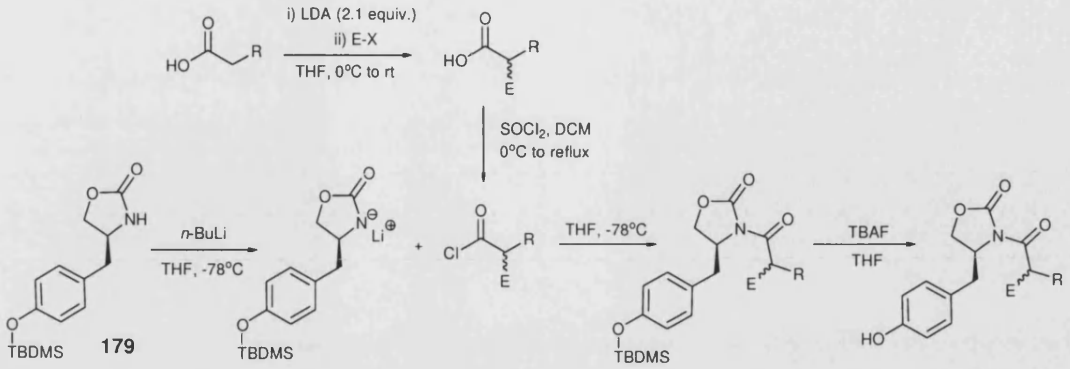
In order to establish the diastereoselectivity of the reactions it was necessary to have authentic samples of the two possible α-alkylated diastereomers in each case. In this array, it was decided that analysis of the diastereomeric products would be carried out by cleavage of the alkylated product resin with 1% TFA since this would afford chiral products containing a 4-benzyl-oxazolidin-2-one fragment with a chromophore that was easily detectable by HPLC with UV detection.

It was therefore necessary to prepare authentic 1:1 mixtures of two possible diastereomeric products of each alkylation reaction in solution phase. The general strategy was to prepare racemic α-alkylated acid corresponding to the desired side-chain, activate it as an acid chloride by refluxing with thionyl chloride ($SOCl_2$) and then use it to *N*-acylate an *O*-benzyl-protected *N*-H oxazolidin-2-one followed by *O*-benzyl deprotection to expose the phenol moiety (scheme 5.1b).



Scheme 5.1b: *General strategy for preparation of 1:1 mixtures of diastereomeric products of enolate alkylation reactions. Appropriate carboxylic acid α-alkylated via treatment with 2.1 equiv. LDA and appropriate electrophile. Racemic α-alkylated acid then activated as acid chloride by refluxing with $SOCl_2$ in DCM and added to lithium anion of N-H oxazolidin-2-one, followed by O-deprotection via catalytic hydrogenation.*

In cases where the electrophile was either benzyl bromide or methyl iodide, the standard *O*-benzyl protected oxazolidin-2-one **103** was employed with the protecting group being removed in a facile, chemoselective manner by catalytic hydrogenation. However, when the electrophile employed was allyl iodide, this protecting strategy could not be employed as the *O*-deprotection conditions would also cause hydrogenation of the alkene functionality. For these substrates, an alternative TBDMS-protected oxaolidin-2-one **179** was prepared by treatment of **1** with TBDMS-Cl using imidazole and DMAP as nucleophilic catalysts. Deprotection was achieved highly selectively by brief treatment with terabutylammonium fluoride (TBAF) (see Scheme 5.1c).



Scheme 5.1c: *Strategy for the preparation of 1:1 mixtures of diastereomeric products of enolate alkylation reactions where the reaction products included an allyl moiety. Appropriate carboxylic acid α-alkylated via treatment with 2.1 equiv. LDA and appropriate electrophile. Racemic α-alkylated acid then activated as acid chloride by refluxing with $SOCl_2$ in DCM and added to lithium anion of O-TBDMS-oxazolidin-2-one, followed by O-deprotection with TBAF.*

The 1:1 mixtures of diastereomers thus gained (see Fig 5.1a) were then used to develop HPLC conditions that caused baseline separation of the two peaks (see experimental procedure for compound-specific details).

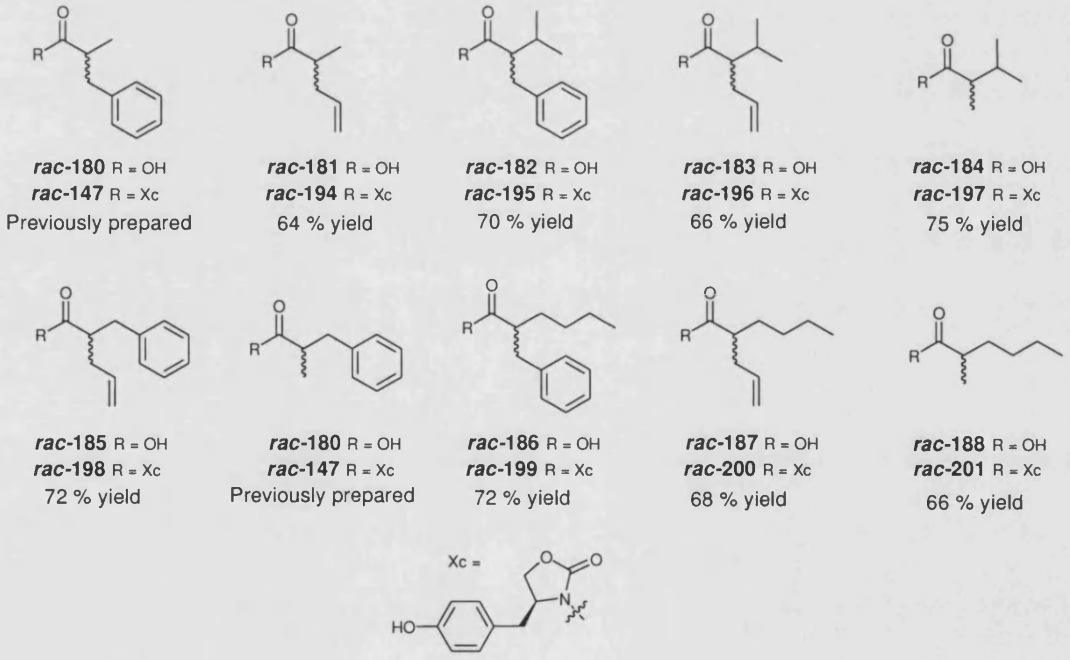
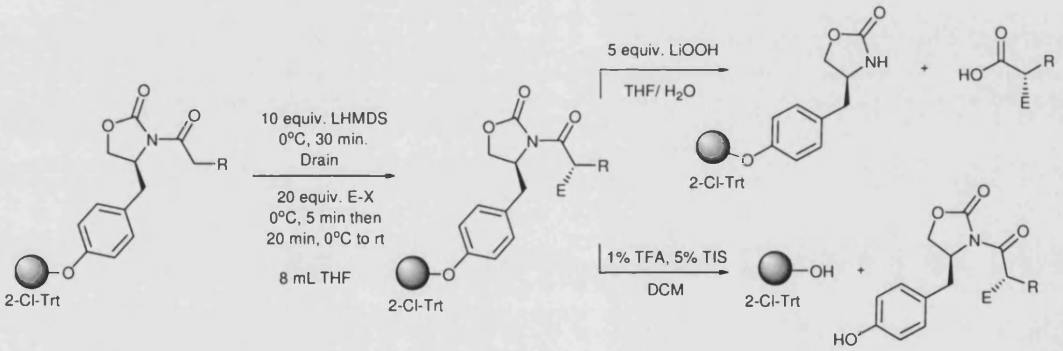


Fig 5.1a: *Pairs of diastereomers that were prepared in 1:1 ratio via solution phase techniques described above, with yield over two steps – N-acylation of protected oxazolidin-2-one with racemic acid and deprotection.* NB: Diastereomers all have configuration 4(*S*)-2-rac-.

Confident that the diastereoselectivity of each polymer supported alkylation reaction could now be determined by HPLC analysis of the mixture of α-alkylated diastereomers resulting from cleavage of the resin with 1% TFA, a series of solid phase asymmetric enolate alkylation reactions were then conducted. Each experiment was carried out using the conditions previously optimised for the *N*-propionyl / benzyl bromide combination (see Scheme 5.1d) with the results being described in Table 5.1a. In each case the reaction was conducted on 150 mg *N*-acyl-oxazolidin-2-one resin and for characterisation purposes following the alkylation reaction, a 20 mg portion of each alkylated resin was treated with 1% TFA and 5% TIS in DCM to cleave the diastereomeric products of the polymer-supported enolate alkylation reaction and allow determination of the de of the alkylated products *via* HPLC analysis. The remaining resin (approx. 130 mg) was then treated with LiOOH (made *in situ* from H_2O_2 and LiOH) in THF / H_2O to hydrolyse the side-chain and afford the corresponding α-alkylated acid that was recovered after acidic aqueous extraction, thus allowing the isolated yield of the reaction to be determined.



Scheme 5.1d: *Reaction conditions for array of enolate alkylation reactions, employing four different solid-supported N-acyl oxazolidin-2-ones and three different electrophiles.*

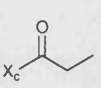
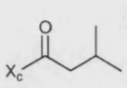
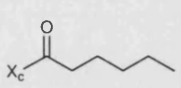
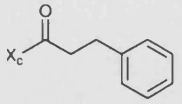
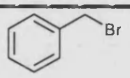
Electrophile	*N*-Acyl oxazolidin-2-one			
				
 Benzyl bromide	**147** 97% de 69% yield	**195** 99% de 52% yield	**199** 90% de 48% yield	N/A
 Allyl iodide	**194** ~ [a] 61% yield	**196** 99% de 60% yield	**200** 99% de 58% yield	**198** ~ [b]
$H_3C—I$ Methyl iodide	N/A	**197** 90% de 42% yield	**201** 95% de 53% yield	**202** 87% de 45% yield [c]

Table 5.1a: ***Table to show de of each of the products of the array of asymmetric solid-supported enolate alkylation reactions and the yield of acid recovered after LiOOH cleavage.*** *Reaction conditions as detailed in Scheme 4.3r. Yield of acid calculated from mass of acid recovered and based upon the calculated loading of N-H oxazolidin-2-one onto 2-Cl-Trt resin thus representing yield over three steps – N-acylation, enolate alkylation and side-chain cleavage. De determined by HPLC analysis of the crude reaction product after TFA cleavage of 20 mg resin with 1% TFA. Where de = 99%, no trace of minor diastereomer could be observed.* [a] *No splitting of the peak for the two diastereomers could be achieved so de was not determined.* [b] *HPLC dominated by unidentified impurity, so no de could be gained.* [c] *Acid product contaminated with 3-phenyl-propionic acid, arising from LiOOH cleavage of unreacted starting material.*

Overall, the results from the array of ten polymer-supported enolate alkylation reactions were successful with each of the acid products being formed in acceptable yields. Although the ee of the resulting acids was not measured due to the lack of UV chromophore in some products rendering them 'invisible' to the UV detector of the HPLC instrument, the de of the preceding diastereomeric products were generally found to be high (87 – 99% de). As it has been shown that the LiOOH cleavage method used proceeds without epimerisation, it can be concluded that the ee values of the acids would be correspondingly high. The reactions employing methyl iodide as electrophile gave slightly lower levels of diastereoselectivity (87 – 95% de) than the analogous reactions employing allyl iodide or benzyl bromide, as expected given its lower steric demands.

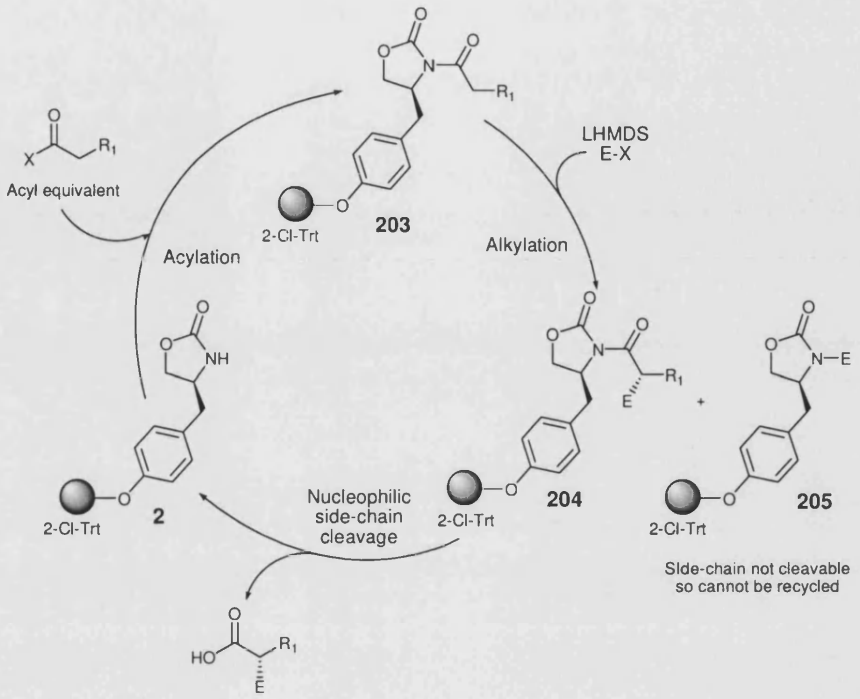
Whilst this series of experiments employed a carefully selected array of *N*-acyl fragments and simple electrophiles, the success of the reaction between the enolate of a polymer-

supported *N*-isovaleryl-oxazolidin-2-one and the relatively unreactive electrophile methyl iodide is particularly noteworthy. It is proposed therefore that the conditions developed for these enolate alkylation reactions should also be applicable to more complex *N*-acyl fragments and more functionalised electrophiles.

To conclude, my optimal reaction conditions developed for the model *N*-propionyl / benzyl bromide system have been shown to be applicable to the enolate alkylation reactions of four different *N*-acyl oxazolidin-2-ones with three different (reactive) electrophiles. As a result nine α-alkylated carboxylic acids were prepared in acceptable yield with good levels of stereocontrol. The results gained here would therefore allow the preparation of useful amounts of chiral α-alkylated products of high ee in quantities adequate for screening purposes.

5.2 Recycling of resin

An important feature of any successful solid-supported chiral auxiliary is its ability to be recycled. This helps to make the overall system more cost-effective after the initial expense of preparing the polymer–supported oxazolidin-2-one is factored into the equation. It had already been demonstrated that recycling of the polymer-supported oxazolidin-2-one **2** should be possible. Reaction conditions had been developed to allow high yielding *N*-acylation, and asymmetric enolate alkylation reactions, with final LiOOH to remove the entire side-chain fragment *via* an exocyclic pathway, regenerating the solid-supported *N*-H oxazolidin-2-one **2** for use in the next cycle (see Scheme 5.2a).



Scheme 5.2a: *Theoretical recycling of solid-supported oxazolidin-2-one* **2**, *including unwanted formation of N-alkyl oxazolidin-2-one* **205** *which cannot be recycled*

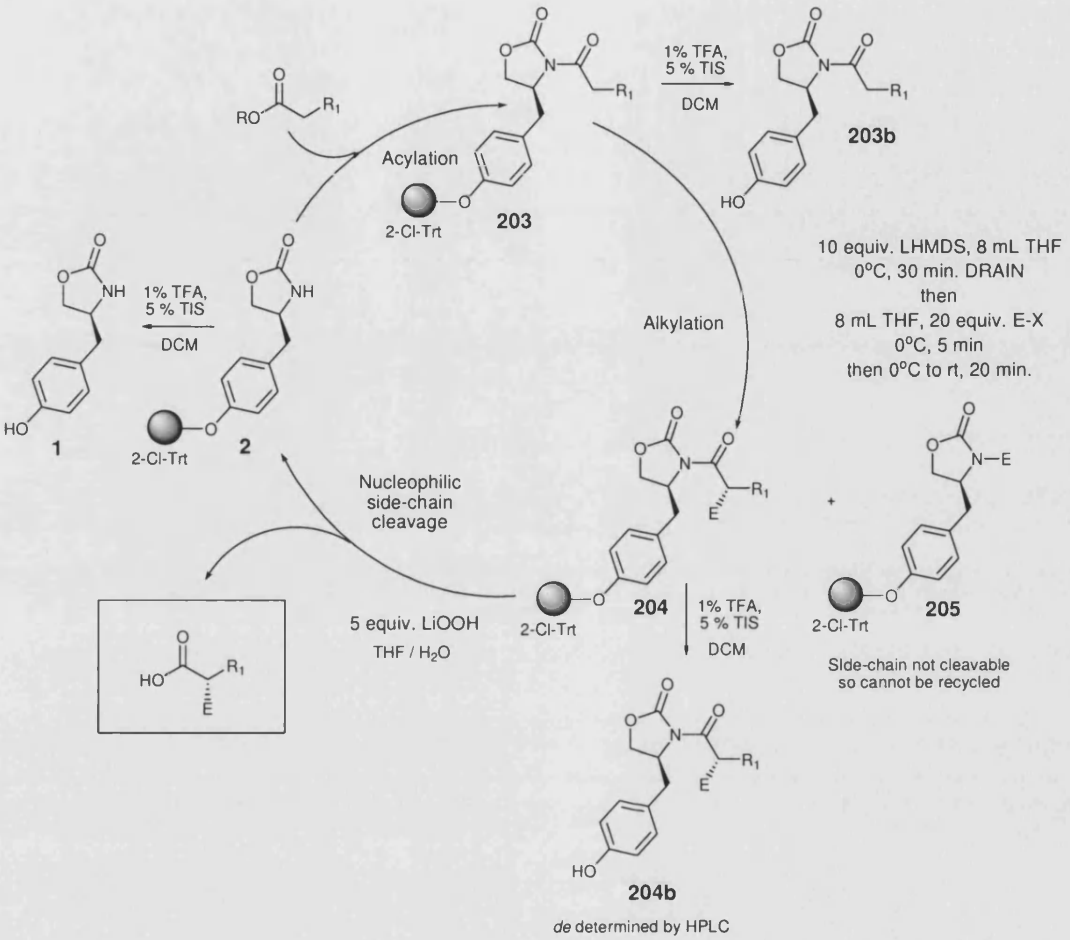
However, one issue that was likely to have a detrimental effect on the recycling process was the possibility of competing formation of *N*-alkyl oxazolidin-2-one **205** from reaction of excess electrophile with the *N*-lithiated oxazolidin-2-one product arising from enolate decomposition. The *N*-alkyl bond of **205** would not be cleaved during the nucleophilic cleavage reaction so would permanently 'cap' the oxazoldin-2-one preventing it from participating in any further enolate alkylation reactions thus reducing the total number of chiral auxiliary fragments available for reaction.

Formation of this type of *N*-alkyl-oxazolidin-2-one species had been minimised by the optimisation process, but as enolate decomposition could not be completely eliminated it was inevitable that a small amount of the *N*-alkyl oxazolidin-2-one (typically $\leq 5\%$ per cycle) would be formed.

A recycling scheme (as represented in Scheme 5.2a) was therefore proposed in which the same batch of resin would be subjected to four sequential reaction cycles. Three of these

cycles would combine a different *N*-acyl-oxazolidin-2-one with a different electrophile, thus allowing any cross-contamination between sequential reaction cycles to be identified. These combinations were selected from the array of enolate alkylation reactions investigated in the previous section as this would allow comparison of yields and de values between the reactions performed on 'recycled' resin and those carried out previously on 'fresh' resin. Additionally, the first and final cycle would employ identical reagents thus allowing for a direct comparison between two identical reactions on the first and fourth cycle of the same batch of resin.

Hence a series of four solid-supported asymmetric enolate alkylation reactions cycles (comprising *N*-acylation, alkylation and side chain cleavage) were conducted on the *same batch* of 2-Cl-Trt-supported oxazolidin-2-one resin, according to the reaction protocols described in Scheme 5.2b and Table 5.2a. Characterisation of the oxazolidin-2-one species was achieved at each stage by cleaving a 20 mg portion of resin with 1% TFA and 5% TIS in DCM. The de of the alkylation reactions was determined by HPLC analysis of the crude diastereomeric oxazolidin-2-one species after cleavage and comparison with authentic samples of 1:1 mixtures of the two possible diastereomers.



Scheme 5.2b: ***Resin recycling investigation***. *Four successive enolate alkylation reaction cycles (comprising N-acylation, enolate alkylation and LiOOH side-chain cleavage) conducted on the same batch of 2-Cl-Trt-supported oxazolidin-2-one* **2** *with different combinations of N-Acyl-oxazolidin-2-ones and electrophiles. N-acylation reactions employed either the appropriate acid or the anhydride according to the standard method detailed in Section 3.3. Enolate alkylation reactions conducted according to the conditions optimised for the model N-propionyl / benzyl bromide reaction, described in Scheme 4.3r. LiOOH side chain cleavage reactions conducted according to Section 3.4.2b. Identification of the oxazolidin-2-one species at each step was conducted via cleavage of the resin with 1% TFA and 5% TIS in DCM followed by ^{1}H-NMR analysis of the crude product.*

Cycle	Acylating agent	R_1	E-X	Diastereomeric Product	de (%) [a] (Previous de%) [b]	Yield of acid (%) [c] (Previous yield %) [d]
1	Propionic anhydride	Me	BnBr	**147**	95 (97)	55 (69)
2	Isovaleric anhydride	$CH(CH_3)_2$	MeI	**197**	87 (90)	40 (42)
3	Hydrocinnamic acid	Bn	Allyl-I	**198**	~ [e]	43
4	Propionic anhydride	Me	BnBr	**147**	96 (97)	38 (69)

Table 5.2a: *Identity of N-acyl-oxazolidin-2-ones and electrophiles in the four cycles of the resin recycling investigation and the corresponding results. Four successive enolate alkylation reaction cycles (comprising N-acylation, enolate alkylation and LiOOH side-chain cleavage) conducted on the same batch of 2-Cl-Trt-supported oxazolidin-2-one* **2** *with different combinations of N-Acyl-oxazolidin-2-one and electrophile.* [a] *De determined by HPLC analysis of the crude reaction product after cleavage of 20 mg resin with 1% TFA.* [b] *Previous de obtained for identical reaction on fresh oxazolidin-2-one resin, see Section 5.1.* [c] *Isolated yield of acid after work-up, based upon the calculated loading of N-H oxazolidin-2-one onto 2-Cl-Trt resin representing yield over three steps – N-acylation, enolate alkylation and side-chain cleavage.* [d] *Previous yield obtained for identical reaction on fresh oxazolidin-2-one resin, see Section 5.1.* [e] *HPLC dominated by unidentified impurity so de could not be determined.*

From the results gained (see Table 5.2a) it appears that 2-Cl-Trt-supported oxazolidin-2-one **2** can be recycled four times with no apparent loss in diastereoselectivity in the enolate alkylation step. In each case, the de obtained was similar to that obtained previously using 'fresh' oxazolidin-2-one resin. To highlight this, the first and fourth cycle employing identical reagents produced essentially identical de values for the production of **147**. However, the yield of the reaction did decrease between each progressive cycle with the combined reactions of the fourth cycle producing a 38% yield for formation of **(*R*)-65** compared to the identical reactions of the first cycle which gave a 69% yield of **(*R*)-65**. Analysis of the *N*-H oxazolidin-2-one **1** after cleavage of a 20 mg portion at the end of each cycle by ^{1}H-NMR, showed an increasingly more complex spectrum between each reaction. The ^{1}H-NMR spectra of the *N*-H oxazolidin-2-one fragments cleaved after the first and fourth cycles are shown in Figs. 5.2a,b. The principle impurities introduced appear to produce peaks in the aromatic region and also between δ 1.0 and 1.5 ppm, which are likely to be a result of resin decomposition. It is also likely that some of the reduction in purity observed was due to the accumulation of small quantities of *N*-alkyl oxazolidin-2-one formed in each alkylation reaction that were not cleaved by treatment with LiOOH.

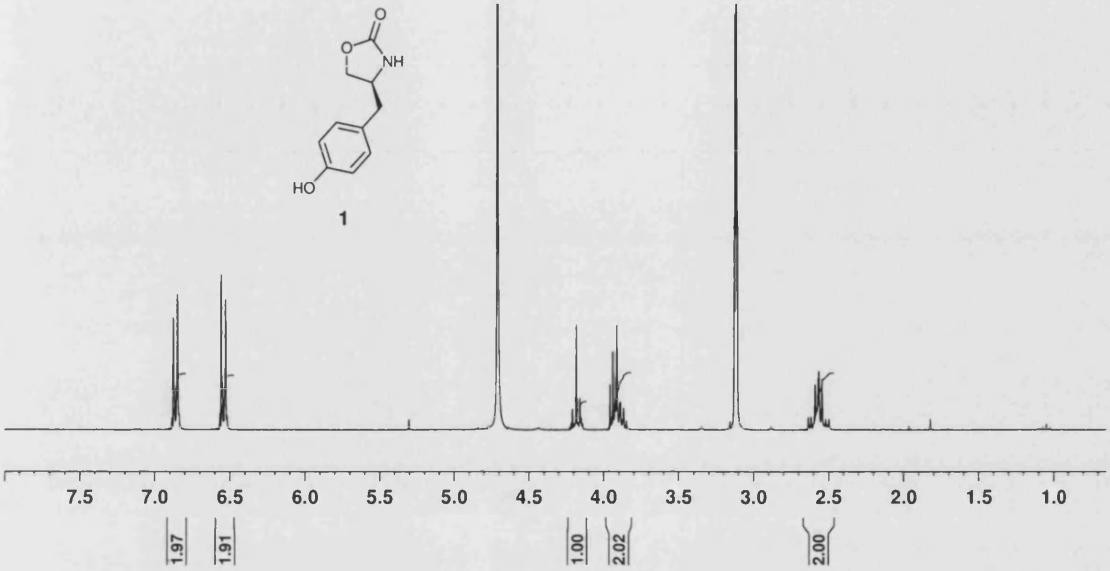


Fig. 5.2a: *^{1}H-NMR spectrum of N-H oxazolidin-2-one fragment* **1** *cleaved from 2-Cl-Trt resin after first reaction cycle i.e. N-acylation, enolate alkylation and LiOOH side-chain cleavage.*

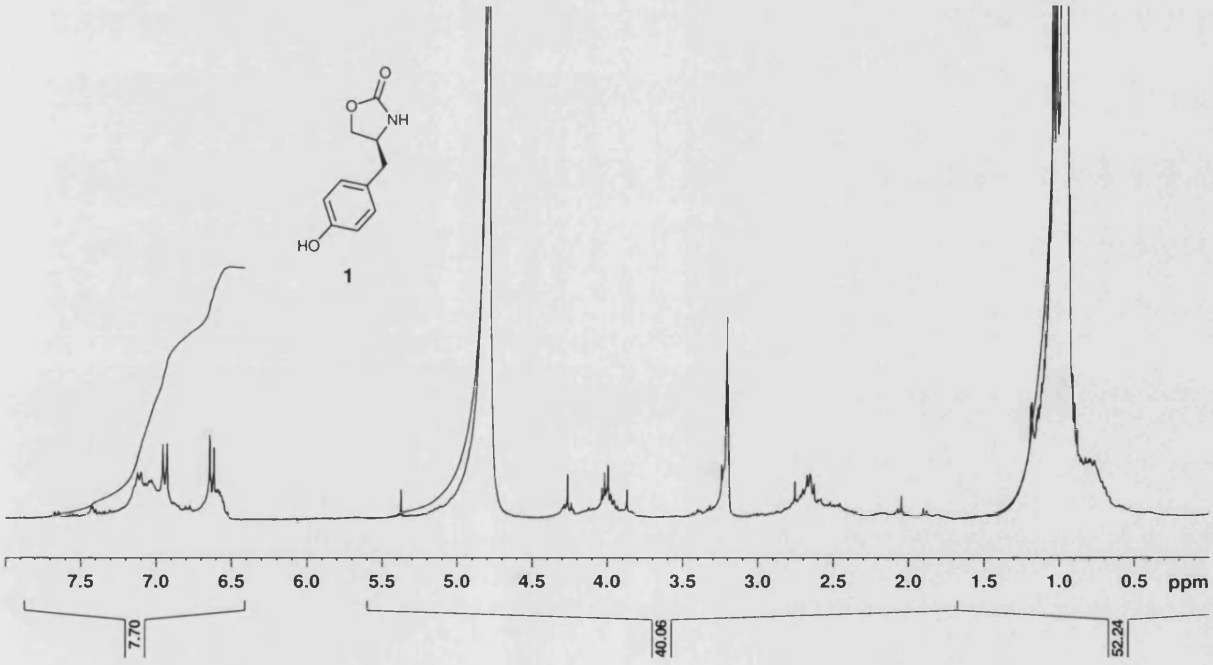


Fig 5.2b: *^{1}H-NMR spectrum of N-H oxazolidin-2-one fragment* **1** *cleaved from 2-Cl-Trt resin after four reaction cycles. Each cycle consists of N-acylation, enolate alkylation and LiOOH side-chain cleavage.*

Importantly there was no evidence of any cross-contamination between products arising from different cycles (see Figs 5.2c,d,e,f). However, the ^{1}H-NMR spectrum of (*R*)-2-benzyl propionic acid **(*R*)-65** produced after the fourth cycle (Fig. 5.2f) was clearly less pure than that produced after the first cycle (Fig. 5.2c). This may imply that even with efficient side-chain cleavage between each cycle, some side-products / contaminants accumulate on polymer-support between each cycle that can contaminate the acidic product of LiOOH side-chain cleavage. However, this effect was not noted until after the third cycle, and the extent of contamination was not large.

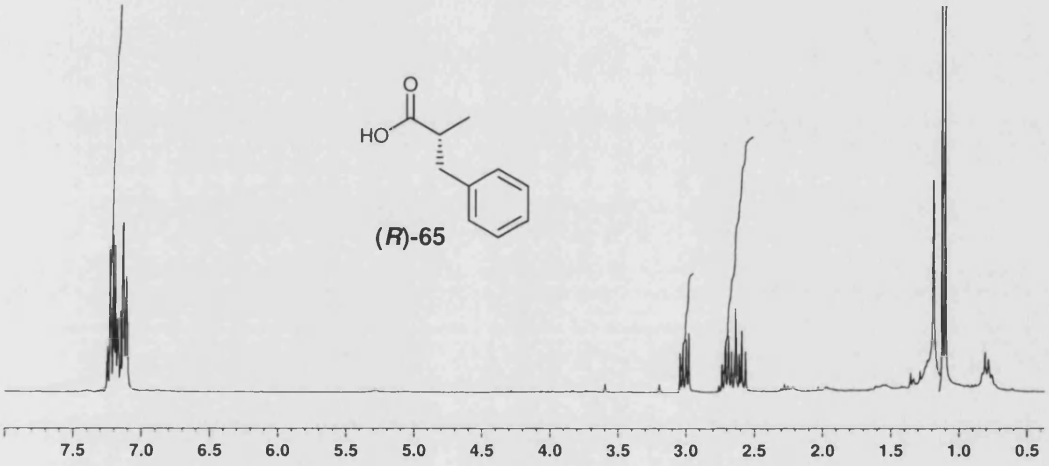


Fig. 5.2c: *^{1}H-NMR spectrum of (R)-2-benzylpropionic acid produced in first cycle of recycling scheme.*

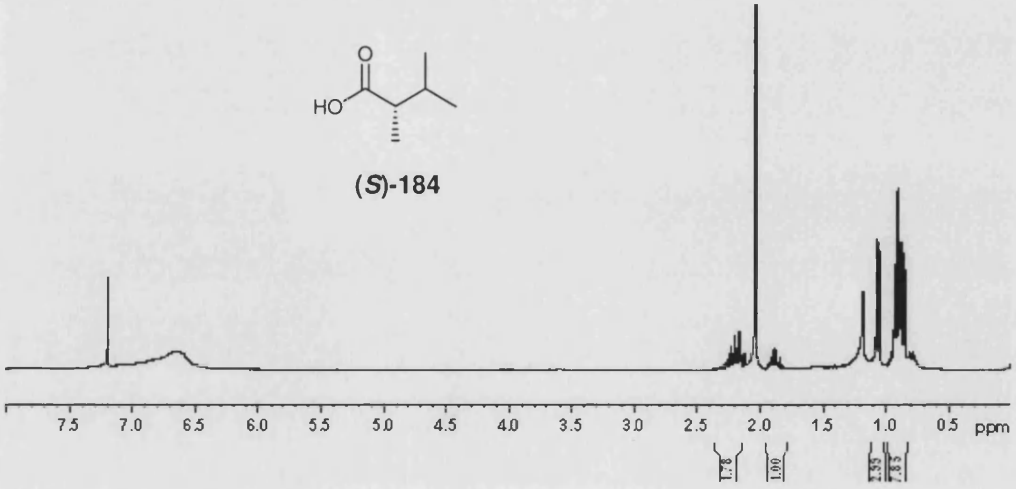


Fig 5.2d: *^{1}H-NMR spectrum of (S)-2,3-dimethylbutanoic acid produced in the second cycle of the recycling scheme.*

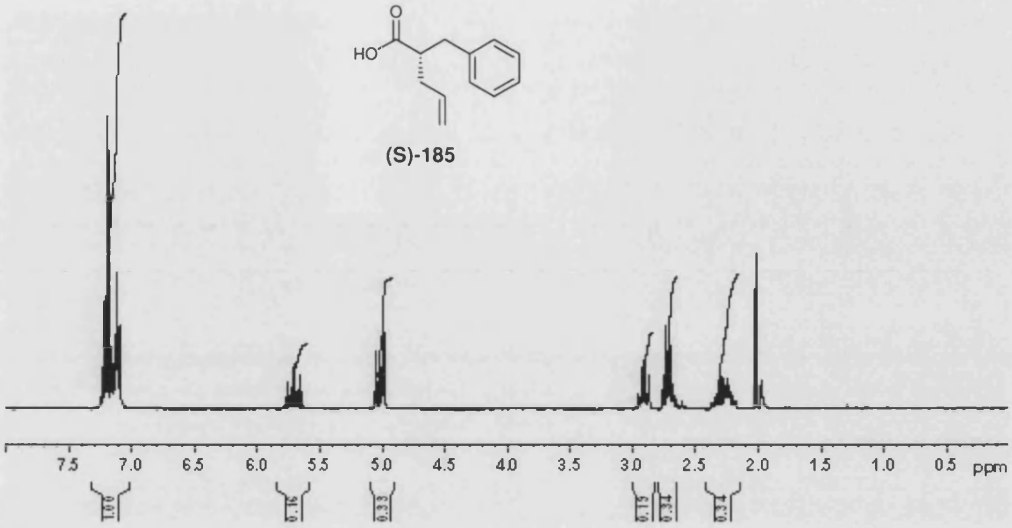


Fig 5.2e: *^{1}H-NMR spectrum of (S)-2-benzylpent-4-enoic acid produced in the third cycle of the recycling scheme.*

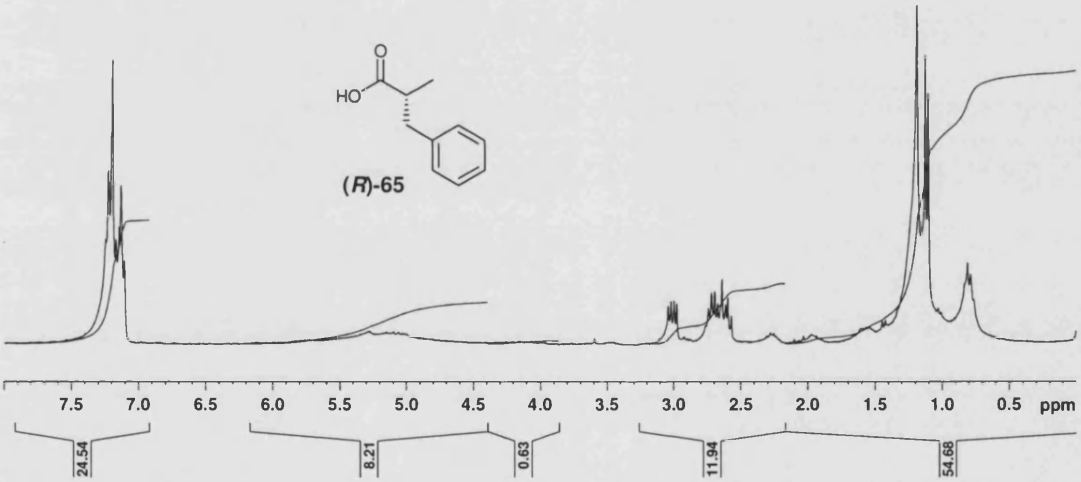


Fig. 5.2f: *^{1}H-NMR spectrum of (R)-2-benzylpropionic acid produced in the fourth cycle of the recycling scheme.*

To conclude, it had been shown that the polymer-supported oxazolidin-2-one **2** could be recycled at least four times without a reduction in stereoselectivity. However, possibly due to the slow accumulation of *N*-alkyl oxazolidin-2-one (as a result of enolate decomposition), the purity of the products produced from polymer-supported oxazolidin-2-one decrease with each cycle. This also leads to a progressive reduction in the isolated yield of the side-chain cleaved acid products between each cycle due to reduction in the

number of *N*-H oxazolidin-2-one fragments available for reaction on polymer support. A reduction in purity of the acid product prepared after the fourth cycle was also observed, however acceptable results were gained for the first three cycles of the resin. Therefore, it is proposed that polymer-supported oxazolidin-2-one **2** may be used at least three times thus increasing its cost-effectiveness significantly.

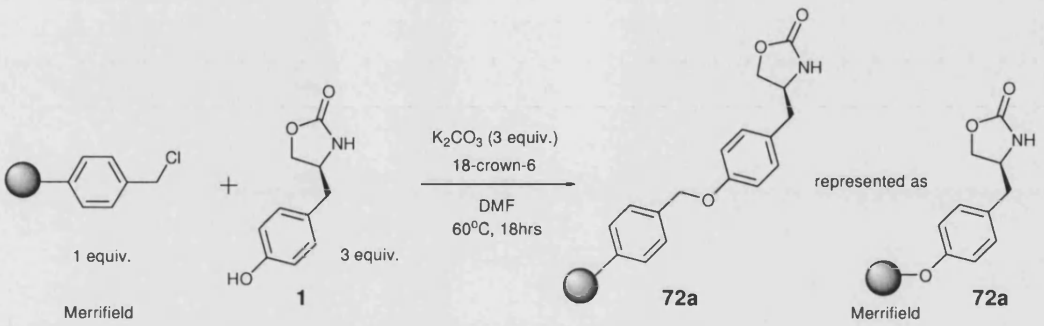
5.3 Development of a Merrifield resin supported oxazolidin-2-one auxiliary

The ultimate aim of this work was to develop a synthetically useful solid-supported oxazolidin-2-one chiral auxiliary that was efficient and user-friendly. In order to decrease the cost even further, it was proposed that the relatively expensive and highly acid-sensitive 2-chlorotrityl-chloride resin might be replaced with cheap, robust Merrifield resin.

As discussed earlier (see Chapter 3.1), Merrifield resin was not considered ideal for the optimisation of reaction conditions as the intermediate α-benzyl-*N*-acyl-oxazoldin-2-one-diastereomers (or enolate decomposition products) could not be easily cleaved for analysis due to the harsh acidic conditions required to cleave the benzylic ether linker of this type of resin. Hence, the only method available to establish the success of the asymmetric enolate alkylation would be *via* side-chain cleavage and determination of the isolated yield and ee of the resulting side chain fragment. It was proposed that the conditions optimised for the 2-chlorotrityl-chloride supported chiral auxiliary **2** might also be applicable to Merrifield supported auxiliary and therefore a second round of extensive method development would not be necessary. However, Burgess had previously reported significantly inferior results when employing a Merrifield-supported oxazolidin-2-one auxiliary for asymmetric enolate alkylation reactions in comparison to a Wang-supported oxazolidin-2-one (50-55% for Merrifield, 85-90% for Wang), thus implying that resin type could dramatically affect the performance of the entire system.[25]

Hence a Merrifield resin supported oxazolidin-2-one auxiliary **72a** was prepared by immobilisation of *N*-H oxazolidin-2-one fragment **1** onto Merrifield resin according to the

method of Hallman *et al.* (see Scheme 5.3a).[89] It should be noted that attempts to employ *N*-propionyl oxazolidin-2-one fragments for immobilisation by this method resulted in *N*-acyl side-chain cleavage under the reaction conditions.



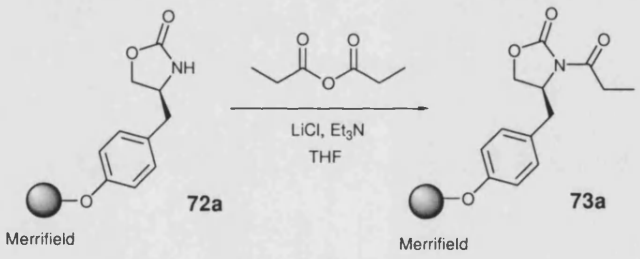
Scheme 5.3a: *Immobilisation of oxazolidin-2-one auxiliary* **1** *onto Merrifield resin.*

IR analysis (KBr disc) of the resin revealed a characteristic carbonyl peak at 1754 cm^{-1} indicating that oxazolidin-2-one had been immobilised onto the resin, but determination of the loading of oxazolidin-2-one auxiliary onto the Merrifield resin was, as anticipated, difficult to establish. Previously the loading of 2-chlorotrityl-chloride resin-bound oxazolidin-2-one had been estimated by the mass of recovered oxazolidin-2-one fragment after acidic cleavage of the linker attaching the auxiliary to the resin. However, for Merrifield resin, the conditions required for complete cleavage of the oxazolidin-2-one fragment were significantly harsher than for 2-chlorotrityl chloride resin. Treatment of oxazolidin-2-one functionalised Merrifield resin **72a** with 50% TFA in DCM for 30 minutes did result in cleavage of some oxazolidin-2-one **1** corresponding to a loading of 0.21 $mmolg^{-1}$ (20%) that was estimated by ^{1}H-NMR analysis after addition of a known amount of crotonic acid as an internal standard. This very low value implied either a low loading of the oxazolidin-2-one onto the resin or incomplete cleavage of the benzylic ether linker. Indeed, repetition of the cleavage process on the same batch of resin afforded more oxazolidin-2-one **1** (approx. 0.014 mmol) giving a total resin loading of 33%. In fact it was found that **1** could still be recovered in low yields after a fourth treatment of the resin with TFA in DCM for 30 minutes. Employing lengthier reaction times involving treatment of a fresh batch of functionalised resin with 50% TFA in DCM for two hours did cleave a greater proportion of oxazolidin-2-one from the polymer, but also gave a significant

quantity of resin-derived impurities. It was therefore concluded that resin loading could not be determined reliably using this cleavage method.

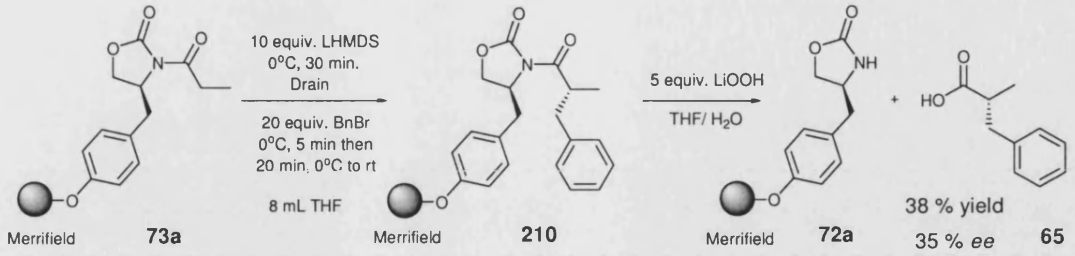
Hence resin loading was estimated roughly by gravimetric analysis involving measurement of the mass gained by the resin in the immobilisation reaction after thorough drying in a vacuum oven for 24 hours at 40 °C. In this way resin loadings of 0.75 – 0.95 $mmolg^{-1}$ were calculated. However, it is important to note that the optimised reaction conditions for the subsequent solid-phase reactions (*N*-acylation, enolate alkylation and side chain cleavage) were such that a large excess of reagents were always employed and hence it was not vital to determine the exact loading of the oxazolidin-2-one fragment onto Merrifield resin.

Acylation of Merrifield supported oxazolidin-2-one **72a** was achieved according to the same procedure described previously for 2-chlorotrityl chloride resin (see Section 3.3) employing propionic anhydride, triethylamine and lithium chloride in refluxing THF (see Scheme 5.3b). Analysis of the resin by IR (KBr disc) revealed the presence of two carbonyl groups (1704 cm^{-1} and 1784 cm^{-1}) indicating that *N*-acylation had occurred.



Scheme 5.3b: *N-acylation of N-H oxazolidin-2-one functionalised resin* **72a** *employing propionic anhydride, triethylamine and lithium chloride*

Alkylation of the enolate of Merrifield-bound *N*-propionyl oxazolidin-2-one with benzyl bromide under the optimised conditions established for the 2-chlorotrityl-supported oxazolidin-2-one **2** (see Scheme 5.3c) afforded 2-benzylpropionic acid in a disappointing 38% yield and 35% ee after LiOOH cleavage. Further repetitions of this experiment did not result in any improvement on these results.



Scheme 5.3c: *Model enolate alkylation reaction performed on Merrifield-supported oxazolidin-2-one* **73a**.

It therefore appears that the type of resin employed as a polymer-support for the *N*-acyl-oxazolidin-2-one fragment has a profound effect on the diastereoselectivity of the asymmetric enolate alkylation reaction. It should be noted that in this investigation, the Merrifield resin employed was 2% DVB-crosslinked rather than the usual 1% DVB-crosslinked resin. It is known that the extra degree of cross-linking in 2% DVB resins results in increased rigidity yet this is normally considered beneficial as it allows more stringent reaction conditions to be used and often results in more reproducible results.[66] However, in hindsight, this extra rigidity may also have interfered with the ability of the polymer-supported enolate to adopt the correct conformation required to attain good levels of diastereoselectivity. Unfortunately no details were provided by Burgess *et al.* as to the degree of cross-linking of the Merrifield resin employed in their study.

Although it was disappointing that the reaction conditions developed for 2-chlorotrityl-resin were not directly transferable to Merrifield resin, the 2-chlorotrityl-supported oxazolidin-2-one system still represents a useful polymer for the preparation of α-alkylated carboxylic acids and their derivatives in acceptable yields.

5.4 Development of a polymer-supported SuperQuat auxiliary

The 2-chlorotrityl polymer-supported Evans oxazolidin-2-one chiral auxiliary described allowed for the preparation of α-alkylated *N*-acyl-oxazolidin-2-ones in high de with subsequent nucleophilic cleavage of the side-chain giving chiral α-alkylated products in high enantiopurity. In order to prepare the carboxylic acid products, it was found necessary

to use LiOOH as the nucleophile rather than LiOH as the latter was found to cause a significant amount of endocyclic cleavage on solid support. Not only did this competing pathway reduce yields of the desired product, the LiOH also destroyed the oxazolidin-2-one ring rendering the chiral auxiliary fragment non-recyclable. It was also possible that repeated treatment of the functionalised resin with LiOOH might be responsible for the accumulation of contaminants observed after 4 reaction cycles on the same batch of resin, as seen during the recycling study (see Chapter 5.2). Additionally, the products prepared in this study were relatively simple structures, and the proportion of cleavage proceeding *via* the endocyclic cleavage pathway is known to increase as the steric demand of the acyl fragment increases, particularly when bulky substituents are present at the α-position.

It was reasoned that a polymer-supported SuperQuat auxiliary might address this potential issue. The family of SuperQuat auxiliaries which includes 5,5-dimethyl oxazoldin-2-one **211**, (see Fig. 5.4a) were originally designed to act as chiral auxiliaries in much the same way as Evans oxazolidin-2-one auxiliaries, but are less prone to endocyclic cleavage. This is due to the C-5 geminal dimethyl substituents blocking the Burgi-Dunitz angle of attack of nucleophiles at the endocyclic carbonyl. The approaching nucleophile is therefore more likely to attack the relatively less-hindered exocyclic carbonyl (see Fig. 5.4a).

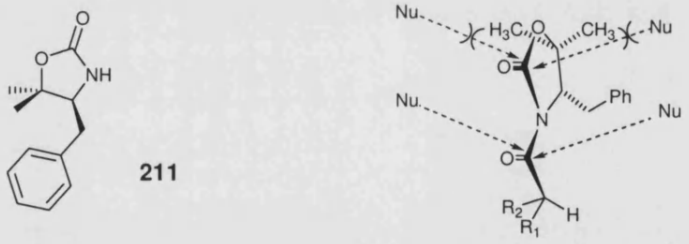
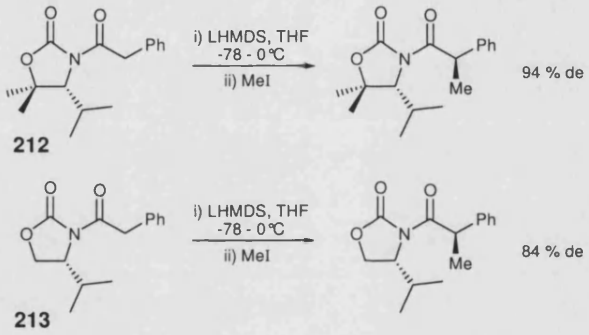


Fig. 5.4a: *a) SuperQuat auxiliary* **211** *and b) SuperQuat auxiliary discourages cleavage at endocyclic carbonyl due to unfavourable steric interactions between the gem-dimethyl substituents at C-5 and the incipient nucleophile.*

Solution phase studies have shown that *N*-acyl-oxazolidin-2-ones derived from the SuperQuat auxiliary do not exhibit any sign of endocyclic cleavage,[90] even for aggressive nucleophiles such as LiOH or NaOH. The use of a polymer-supported SuperQuat-oxazolidin-2-one auxiliary would therefore potentially eliminate the need to use LiOOH in

the preparation of carboxylic acids and ensure complete selectivity during nucleophilic cleavage for the exocyclic carbonyl. A further advantage of SuperQuat auxiliaries is their ability to be cleaved using DIBAL-H to allow direct preparation of aldehyde side-chain products.[91] This is in contrast to Evans oxazolidin-2-ones, where attempts to perform DIBAL-H cleavage results in extensive endocyclic cleavage. Finally it has been claimed that higher diastereoselectivities can be gained using SuperQuat auxiliaries for enolate alkylation reactions in solution phase when compared to their Evan's-style counterparts. For example, comparative studies involving methylation of the enolates of *N*-acyl-5,5-dimethyl-4-isopropyloxazolidin-2-one **212** and the corresponding Evans-type analogue **213** (see Scheme 5.4a) [92] revealed a significantly higher de for the SuperQuat system.



Scheme 5.4a: *Enolate alkylation reactions of N-acyl-5,5-dimethyl-4-isopropyloxazolidin-2-one* **212** *and the corresponding Evans-type analogue* **213** *in which a higher level of diastereoselectivity is achieved for SuperQuat* **212** *compared to Evans-type auxiliary* **213**.

It was shown by nOe studies, that in SuperQuat derived *N*-acyl-oxazolidin-2-ones, steric interactions between its C-5 dimethyl substituent and the methyl groups of the C-4 isopropyl substituent, results in one of the methyl groups of the isopropyl group being orientated directly beneath the plane of the enolate (conformer II) (see Fig. 5.4b). This effect is more pronounced than in the corresponding Evans-type auxiliary where there is reduced steric interaction due to the smaller C-5 substituents and hence conformer II is less favoured. In both cases, conformer II is more effective at blocking electrophilic attack from the bottom face and therefore the SuperQuat chiral auxiliary results in improved diastereoselectivity.[82]

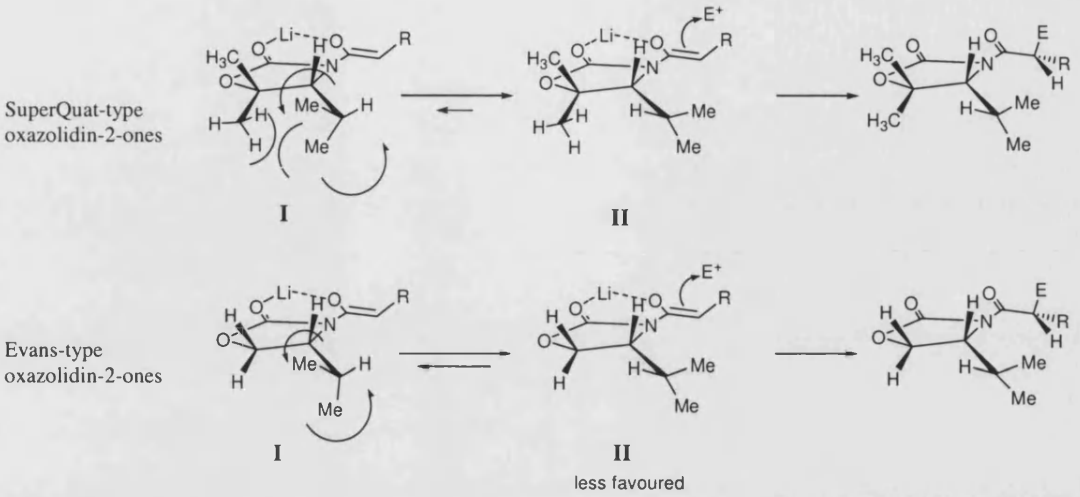
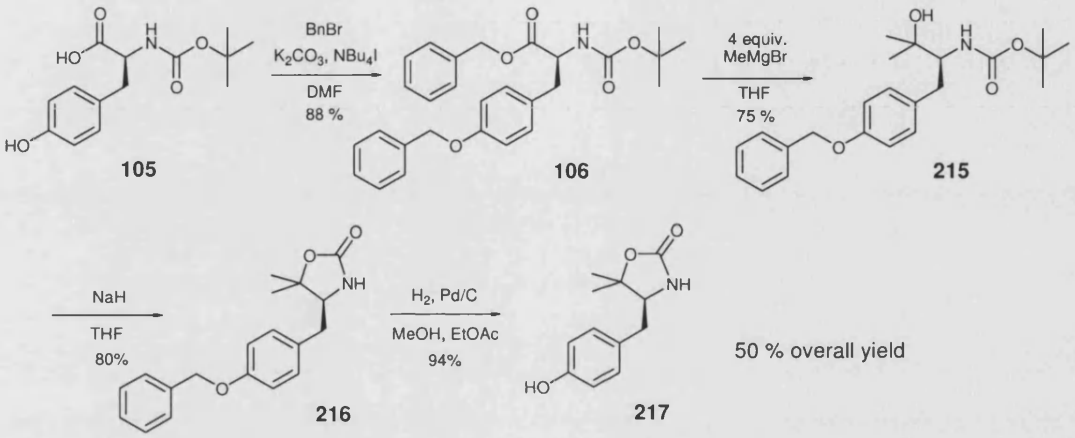


Fig 5.4b: *Rationale behind the improved diastereoselectivity that has been observed for 5,5-dimethyl oxazolidin-2-one (SuperQuat) auxiliaries when compared to their Evans oxazolidin-2-one counterparts. Steric hindrance between the C-5 syn methyl group and the C-4 methyl substituents of the isopropyl group results in positioning of the methyl groups directly beneath the enolate, thus providing greater steric hindrance to the approaching electrophile and increasing diastereoselectivity.*

However, it has also been reported that the enolate of 5,5-dimethyl-oxazolidin-2-one was less stable than that of the corresponding Evans oxazolidin-2-one and was therefore more prone to decomposition which would result in lower yields of desired α-alkylated product on polymer support. Therefore, in order to investigate these effects, a polymer-supported SuperQuat auxiliary was prepared and its application to enolate alkylation reactions investigated.

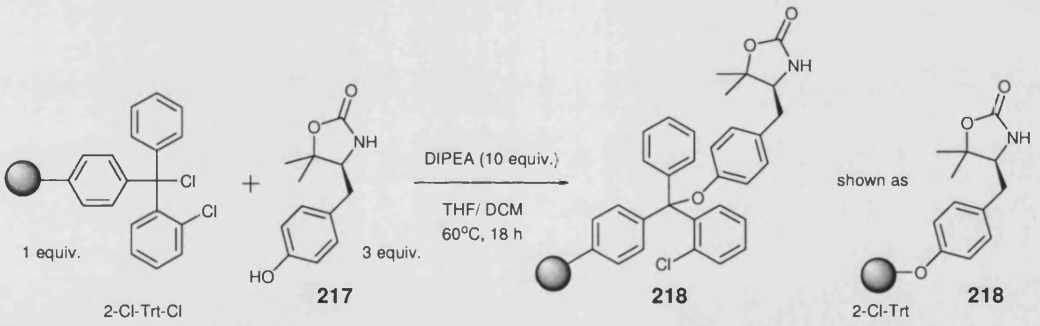
A SuperQuat auxiliary fragment **217** suitable for immobilisation onto resin was easily prepared (Scheme 5.4b) by variation of the procedure previously used for the preparation of the Evans oxazolidin-2-one fragment **1** (see Section 2.2.1). Hence, *bis*-benzylated *N*-Boc tyrosine **106** was prepared by treatment of *N*-Boc tyrosine **105** with an excess of benzyl bromide and potassium carbonate. The introduction of a *gem*-dimethyl groups was easily achieved by treatment of the benzyl ester with 4 equiv. of methylmagnesium bromide to form gem-dimethyl alcohol **215**. As before, attack of the alkoxide (formed by deprotonation of the alcohol with NaH) onto the carbonyl of the Boc group results in formation of the oxazolidin-2-one ring **216**. Finally, catalytic hydrogenation to remove the

benzyl ether protecting group exposes the phenol group necessary for immobilisation to afford SuperQuat oxazolidin-2-one **217** in an overall 50% yield.



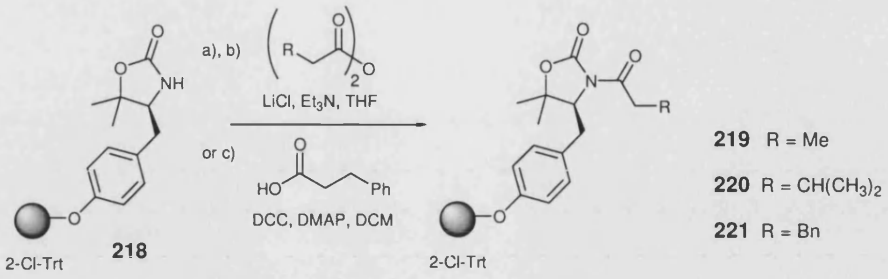
Scheme 5.4b: *Synthesis of SuperQuat (5,5-dimethyl oxazolidin-2-one) auxiliary fragment.*

Immobilisation of **217** onto 2-chlorotrityl chloride resin proceeded as before (see Section 3.2) with a loading of 1.06 mmolg^{-1} (88% yield) being determined as described previously *via* TFA cleavage (Scheme 5.4c).



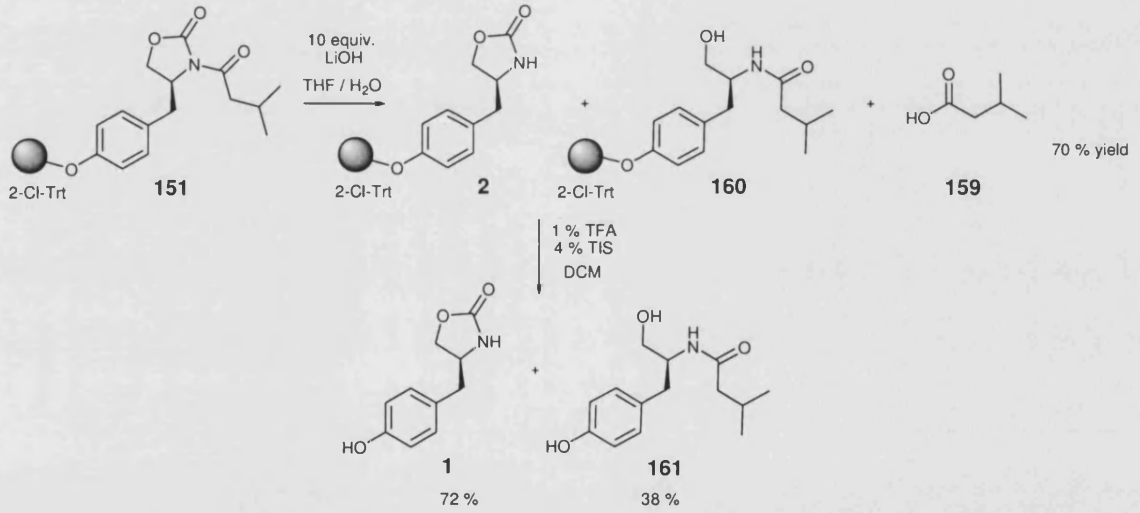
Scheme 5.4c: *Immobilisation of SuperQuat auxiliary fragment* **217** *onto 2-chlorotrityl chloride resin. Loading estimated by mass of recovered auxiliary after TFA cleavage of an aliquot of resin.*

Acylation of the polymer bound 5,5-dimethyl oxazolidin-2-one with propionic or isovaleric anhydride (with triethylamine and lithium chloride) or hydrocinnamic acid (with DCC and DMAP) (Scheme 5.4d) also proceeded smoothly and in comparable yield to the Evans oxazolidin-2-one analogue described previously (**219** 92% yield, **220** 90% yield, **221** 85% yield).

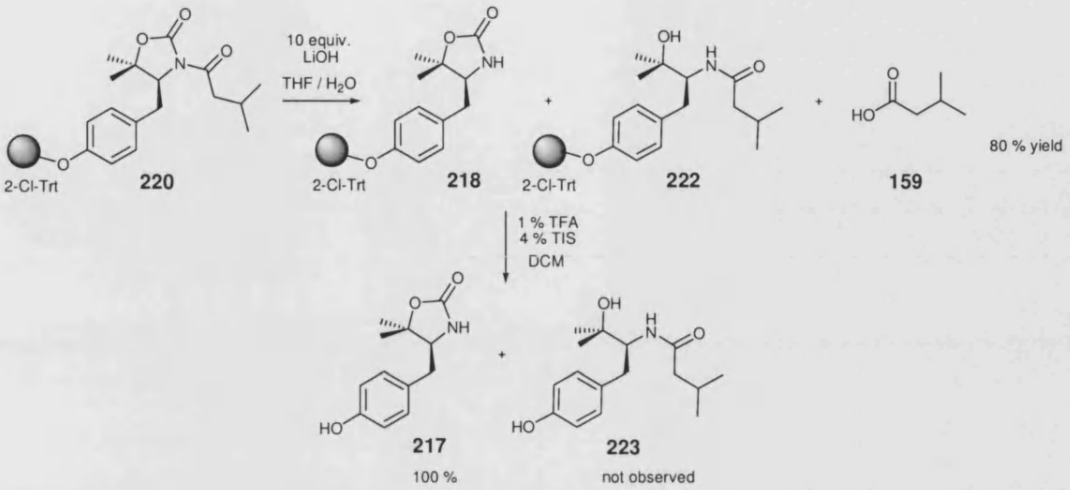


Scheme 5.4d: *N-acylation of 5,5-dimethyl-oxazolidin-2-one with a) propionic anhydride or b) isovaleric anhydride, triethylamine and lithium chloride or c) 3-phenylpropionic acid, DCC and DMAP.*

To confirm that the solid-supported *N*-acyl-5,5-dimethyl oxazolidin-2-one was not prone to endocyclic cleavage, a nucleophilic side chain cleavage reaction employing 10 equivalents of LiOH was conducted. Under these conditions it had previously been noticed that the solid-supported Evans-type *N*-isovaleryl-oxazolidin-2-one **151** underwent significant endocyclic cleavage resulting in reduced yields of the acid product and destruction of the oxazolidin-2-one ring (see Scheme 5.4e).



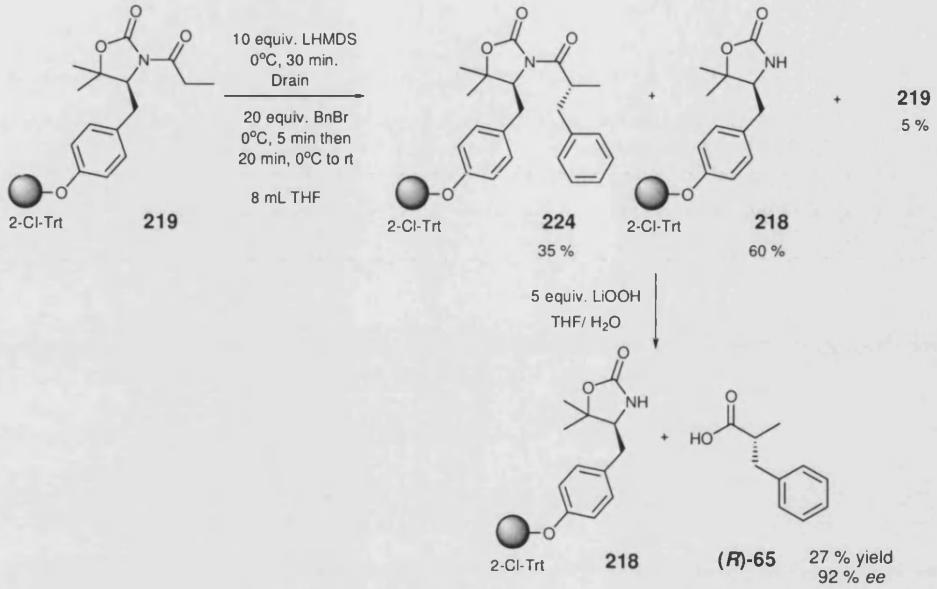
Scheme 5.4e: *Nucleophilic side chain cleavage of solid-supported N-isovaleryl-oxazolidin-2-one* **151** *with 10 equivalents of LiOH.*



Scheme 5.4f: *Nucleophilic side chain cleavage of solid-supported N-isovaleryl-5,5-dimethyloxazolidin-2-one* **220** *with 10 equivalents of LiOH.*

Therefore, solid supported *N*-isovaleroyl 5,5-dimethyloxazolidin-2-one **220** was prepared by *N*-acylation of 5,5-dimethyloxazolidin-2-one **218** using isovaleric anhydride (see Scheme 4.6.2d) with TFA cleavage of an aliquot of the resin showing *N*-acylation had proceeded with 90% yield. Resin **220** was then treated with 10 equivalents of LiOH for 12 hours to afford isovaleric acid in 80% yield (see Scheme 5.4f). Cleavage of the residual resin with 1% TFA in DCM to remove the entire oxazolidin-2-one fragment from the resin revealed the exclusive presence of 5,5-dimethyloxazolidin-2-one with no sign of any *N*-acyl-β-amino alcohol **223** resulting from endocyclic cleavage. Therefore this provides conclusive evidence that SuperQuat derived *N*-acyl-oxazolidin-2-ones afford superior cleavage properties to their corresponding Evans' type oxazolidin-2-ones

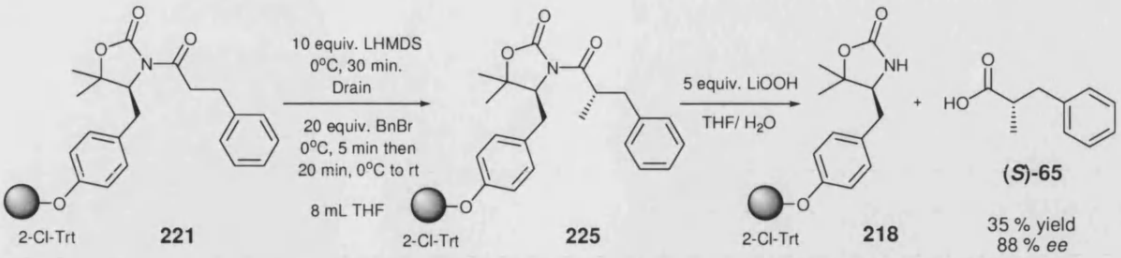
Alkylation of the enolate of polymer-supported SuperQuat-*N*-propionyl-oxazolidin-2-one with benzyl bromide, according to the conditions optimised for the polymer-supported Evans-type oxazolidin-2-one (see Scheme 5.4g) afforded (*R*)-2-benzylpropionic acid (***R***)-**65** in poor yield (27%) but good ee (92%). Examination of the crude reaction product from 1% TFA cleavage of an aliquot of the alkylated resin revealed predominantly *N*-H SuperQuat-oxazolidin-2-one **217** (approx. 60%) with a trace of *N*-propionyl SuperQuat-oxazolidin-2-one **219** starting material and approximately 35% of the desired α-benzylated product **224**.



Scheme 5.4g: *Enolate alkylation reaction of solid supported N-propionyl-5,5-dimethyl-oxazolidin-2-one* **219** *with benzyl bromide, according to the method optimised earlier for the model transformation.*

This reaction clearly demonstrated a considerably greater proportion of *N*-H oxazolidin-2-one (60%) than for the corresponding Evans-type oxazolidin-2-one reaction (20%) suggesting that the enolate of the solid-supported SuperQuat 5,5-dimethyl-oxazolidin-2-one was less stable and more prone to decomposition (as had been reported previously in solution phase).[92] However, the stereoselectivity achieved was similar for the two examples, (92% ee for SuperQuat and 95% ee for Evans), hence there is no evidence in this case of an improved diastereoselectivity for SuperQuat chiral auxiliary **218** arising from the presence of its gem-dimethyl C-5 substituents (see Fig. 5.4b)

To further examine the issue of improved diastereoselectivity, a second reaction was attempted using methyl iodide that had been shown to proceed with the lowest diastereoselectivity using our 2-chlorotrityl immobilised Evans-type oxazolidin-2-one. Hence, the enolate of polymer-supported *N*-3-phenylpropionyl 5,5-dimethyl-oxazolidin-2-one **221** was alkylated under similar conditions using methyl iodide, and the de/ee of the resultant polymer-supported products analysed in the usual manner (see Scheme 5.4h).



Scheme 5.4h: *Enolate alkylation reaction of solid supported N-3-phenylpropionyl-5,5-dimethyl-oxazolidin-2-one* **221** *with methyl iodide, according to the method optimised earlier for the model transformation.*

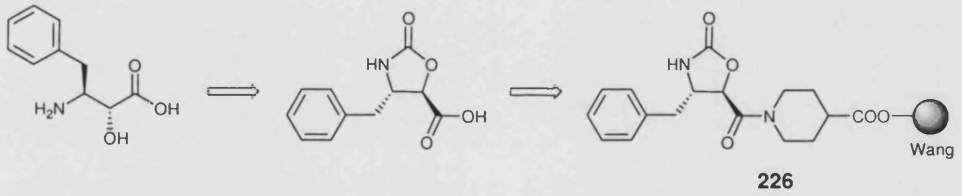
Again, there appeared to be no significant difference in the level of stereocontrol observed (SuperQuat 88% ee, Evans 87% ee) with the isolated yield obtained for (*S*)-2-benzylpropionic acid being lower for the SuperQuat-style chiral auxiliary (SuperQuat 35% yield, Evans 45% yield), once again implying a greater extent of enolate decomposition. This was confirmed by examination of the crude reaction product arising from 1% TFA cleavage of an aliquot of the α-benzylated SuperQuat resin revealed that a large amount of *N*-H SuperQuat-oxazolidin-2-one **218** (approx. 50%) with a trace of *N*-3-phenylpropionyl SuperQuat-oxazolidin-2-one **221** starting material with only 40% of the desired alkylated product **225**.

These initial results suggest that a polymer-supported SuperQuat chiral auxiliary e.g. 5,5-dimethyl-oxazolidin-2-one **218** can be applied to asymmetric enolate alkylation reactions and result in high levels of diastereoselectivity. However, it appears that the yields of chiral products obtained are lower than those achieved for the corresponding solid-supported Evans oxazolidin-2-one discussed earlier, presumably due to increased enolate decomposition of the SuperQuat based system. Early results would therefore suggest that the use of a polymer-supported SuperQuat does not represent an improvement to the solid-supported Evans oxazolidin-2-one system developed earlier. However, the solid-supported SuperQuat auxiliary would potentially have an advantage in some applications if the polymer supported α-alkylated *N*-acyl-oxazolidin-2-one product has a tendency to undergo endocyclic cleavage under nucleophilic side chain cleavage conditions. In addition, the option of using LiOH hydrolysis for side chain removal could offer advantages if the intent was to recycle the functionalised resin, as LiOH cleavage is reported to cause less

decomposition of the polymer support and hence cleaner products compared to LiOOH hydrolysis.

5.5 An alternative polymer-supported oxazolidin-2-one for asymmetric enolate alkylations

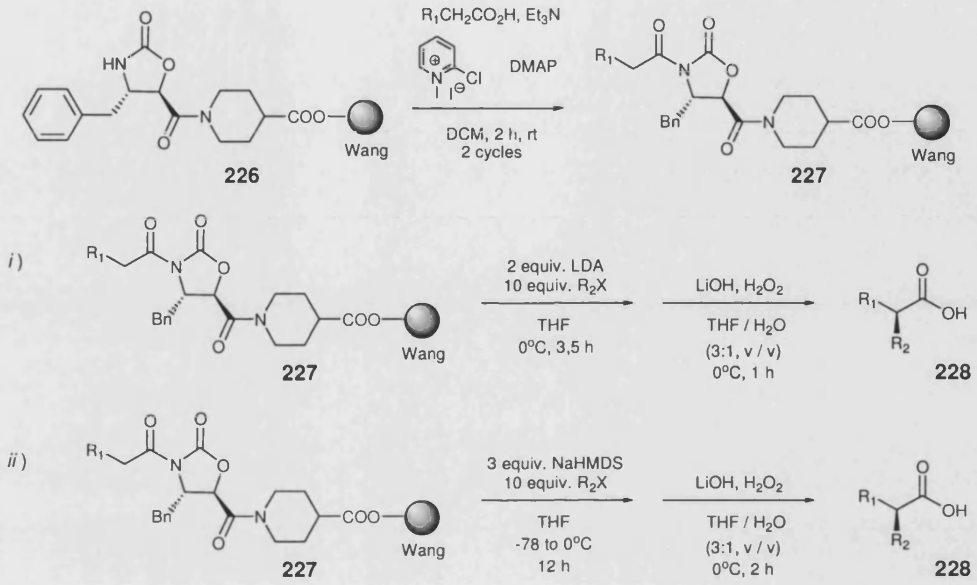
Whilst this work was underway, an account on the use of an alternative polymer-supported oxazolidin-2-one auxiliary **226** for enolate alkylation reactions was reported by Kotake *et al.*[93] Initially a brief communication on this work appeared which was shortly followed by a full paper.[94] Kotake *et al.* proposed that the difficulties experienced by others in achieving high levels of diastereoselectivity in asymmetric enolate alkylation reactions was due to the attachment of the oxazolidin-2-one auxiliary to the polymer support *via* the "critical chiral discriminating unit", *i.e.* the bulky C-4 substituent. Hence they proposed a novel polymer-supported oxazolidin-2-one in which the C-4 substituent was liberated from the polystyrene backbone of the resin by attachment of the oxazolidin-2-one to the polymer support *via* the C-5 position (see Scheme 5.5a).



226

Fig 5.5a: *Design of a new oxazolidin-2-one auxiliary anchored at the 5-position developed by Kotake et al.*

The reaction conditions employed for the solid-supported asymmetric enolate alkylation of oxazolidin-2-one **226** changed completely between their two published reports. In the earlier communication a Wang-supported oxazolidin-2-one resin **227** was treated with 2 equivalents of LDA at 0 °C for 30 minutes before addition of 10 equivalents of the electrophile and stirring at 0 °C for a further three hours (see Scheme 5.5a, *i*). In the second paper, 3 equivalents of NaHMDS were employed for enolate formation at -78 °C for 1 hour, before addition of 10 equivalents of the electrophile and stirring for 12 hours with gradual warming to 0 °C (see Scheme 5.5a, *ii*).



Scheme 5.5a: *N-acylation of solid-supported oxazolidin-2-one* **226** *followed by i) 1st generation enolate alkylation employing 2 equivalents of LDA at 0 °C for 3.5 hours* [93] *and ii) 2nd generation enolate alkylation employing 3 equivalents of NaHMDS at -78 °C to 0 °C for 12 hours.*[94]

Entry	R_1	R_2X	*Yield (%)* [a]		*ee (%)* [b]	
			1st Gen.	2nd Gen.	1st Gen.	2nd Gen.
1	Bn	MeI	48	61	85	85
2	Bn	EtI	-	50	-	88
3	Bn	Allyl I	54	68	96	96
4	Me	BnBr	40	70	97	97
5	Me	4-NO_2BnBr	-	55	-	97

Table 5.5a: *Selected solid-phase enolate alkylation results from both 1st (2004) and 2nd (2005) generation reactions.* [a] *Combined yield of three steps starting from oxazolidin-2-one resin* **226**. [b] *Determined by chiral HPLC analysis after conversion to the corresponding (S)-α-methylbenzylamine-derived amides.*

Significantly higher yields were reported for the revised conditions employing NaHMDS, presumably because the sodium enolates of *N*-acyl-oxazolidin-2-ones **227** at -78 °C were less prone to decomposition than the corresponding lithium enolates at 0 °C. However, the sodium enolates were still prone to enolate decomposition as demonstrated by the observation of approximately 8% *N*-allyl oxazolidin-2-one in the allylation reaction of *N*-3-phenylpropionyl oxazolidin-2-one with allyl iodide, after cleavage of the auxiliary fragment

from the resin *via* methanolysis (see Table 5.5a, entry 3). The de values gained were also very high and roughly in accordance with the values observed in our studies.

In conclusion, Kotake *et al.* have reported on a successful polymer-supported oxazolidin-2-one with a novel anchoring strategy. However, the unnatural amino acid phenylnorstatine from which this oxazolidin-2-one is prepared is very expensive and not readily available, making this polymer-supported oxazolidin-2-one expensive to prepare. In addition, formation of the unwanted *N*-alkyl oxazolidin-2-one during the enolate reaction (as in our system) reduces the ability to recycle the resin. Excellent levels of diastereoselectivity were gained, although the assessment that this was due to attachment through the 5-position does not appear to be accurate since their de values are similar to those observed in our studies employing an oxazolidin-2-one attached to the polymer through its 4-position. It would therefore be interesting to investigate whether alkylation of the enolate of this oxazolidin-2-one **226** with removal of excess base before addition of electrophile might enable even better diastereoselectivities to be achieved for small electrophiles such as methyl iodide.

5.6 Conclusions

Following the successful development of reaction conditions for the asymmetric alkylation of the enolate of polymer-supported *N*-propionyl-oxazolidin-2-one **145** with benzyl bromide (as described in Chapter 4), this chapter focused on exploring and expanding the scope of this reaction.

Firstly it was demonstrated that the optimised reaction conditions could also be applied to other *N*-acyl-oxazolidin-2-ones and other electrophiles. A small array of nine α-substituted acids was prepared, each in reasonable yield and high de, suggesting that this method could allow the preparation of useful amounts of chiral α-alkylated carboxylic acid derivatives in quantities sufficient for screening purposes.

It was further demonstrated that *N*-H-oxazolidin-2-one resin **2** could be reused in asymmetric enolate alkylation reactions three times without loss in diastereoselectivity. However, there was a slight decrease in yields between the cycles, presumably due to the build up of non-cleavable *N*-alkyl oxazolidin-2-one 'blocking' reactive sites. There was also a decrease in purity of the acid products gained, although acceptable purities were achieved in the first three cycles. The potential to recycle the *N*-H-oxazolidin-2-one resin significantly increases its cost-effectiveness.

In a further effort to increase the cost-effectiveness of the polymer-supported chiral auxiliary system, inexpensive Merrifield resin was used as the polymer support. However, disappointing results were achieved with levels of stereocontrol greatly decreased compared to the chlorotrityl-supported analogue. It was therefore concluded that direct transfer of the optimised conditions for the chlorotrityl-supported resin was not possible and further studies would be needed to develop a successful Merrifield-supported version.

Finally, it was demonstrated that polymer-supported SuperQuat oxazolidin-2-ones could also be applied to asymmetric enolate alkylation reactions and achieve high levels of diastereoselectivity. However, the yields gained were inferior to those afforded by the analogous Evans-oxazolidin-2-one auxiliary, seemingly due to an increased propensity towards enolate decomposition in the SuperQuat system. Despite this, a polymer-supported SuperQuat might prove useful in cases where its superior cleavage properties (*i.e* a resistance to endocyclic cleavage) were required.

Overall, this chapter has shown that the solid-supported *N*-H-oxazolidin-2-one system developed in Chapter 4 has the potential to be a useful method to synthetic chemists interested in preparing small quantities of small, chiral compounds in high ee. The potential for resin recycling greatly increases the cost-effectiveness of the system.

Chapter 6 Novel strategies for asymmetric synthesis employing oxazolidin-2-one auxiliaries.

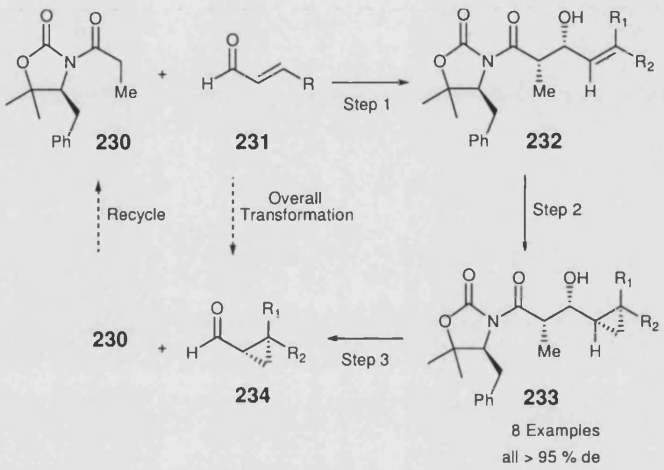
Overview

6.1 Introduction

There is currently ongoing research within the SDB research group into new strategies for the use of chiral auxiliaries. One such strategy is the use of 'temporary' stereogenic centres as stereodirecting groups to create remote stereocentres using substrate-directable reactions. In this approach, a chiral auxiliary is first employed to create a chiral intermediate containing a new stereogenic centre in high de. This new stereocentre is subsequently used to control the facial selectivity of a second, substrate-directable asymmetric reaction thus creating further stereogenic centres. The second chiral intermediate can then either be cleaved to afford the chiral auxiliary and a chiral product or the auxiliary can be left in place to act as a protecting group for a number of subsequent synthetic steps. In this way, the chiral auxiliary acts to create a remote stereocentre beyond its usual sphere of influence.

One example of this reaction strategy employs an oxazolidin-2-one-mediated asymmetric aldol reaction to create a stereodefined hydroxyl group with generally high levels of

diastereoselectivity, with subsequent use of this hydroxyl group to direct further asymmetric reactions. One such example was recently reported by Cheeseman *et al.* in which a novel aldol/cyclopropanation/retro-Aldol strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes in good de was described (see Fig 6.1a). [95]



R_1	R_2	de of **233*** (%)	Yield of **233** (%)
H	Ph	> 95	95
H	*n*-C_8H_{17}	> 95	89
H	*p*-PhOMe	> 95	90
H	*o*-$PhNO_2$	> 95	90
H	2-Furyl	> 95	92
n-C_5H_{11}	H	> 95	96
H	Me	> 95	95
Me	Me	> 95	92

* As determined by ^{1}H-NMR analysis

Fig 6.1a: *Aldol/cyclopropanation / retro-aldol strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.*

In this strategy, chiral auxiliary **230** reacts with an α,β-unsaturated aldehyde **231** to afford a *syn*-aldol product **232** that incorporates a chiral allylic alcohol functionality (Step 1). The 'temporary' β-hydroxyl functionality is then used to control facial selectivity in a directed cyclopropanation reaction to afford cyclopropane **233** in very high de (Step 2). *Retro*-aldol cleavage of cyclopropane **233** results in destruction of the 'temporary' β-hydroxyl

stereocentre, affording the chiral auxiliary fragment **230**, and the desired enantiopure cyclopropane carboxaldehyde **234** in high de. (Step 3).

Following the success of this example, further research was undertaken within the group to investigate the scope of this strategy. It was noted that chiral intermediate **235** was a versatile substrate that could be employed in other asymmetric substrate-directed reactions, for example substrate-directed hydrogenations and epoxidations, as well as cyclopropanations.

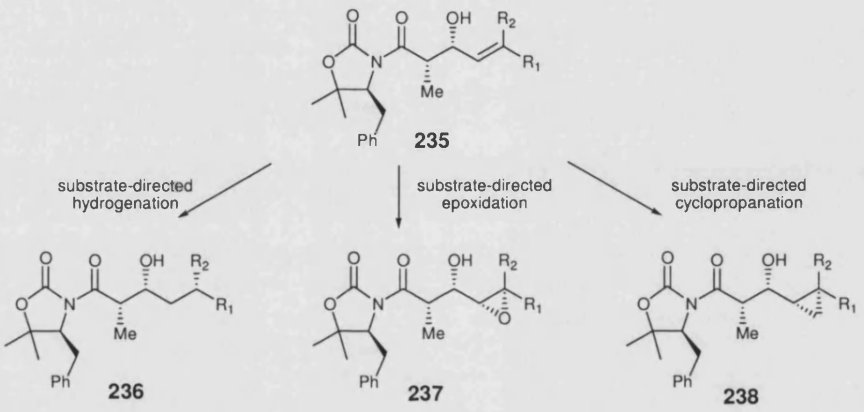


Fig 6.1b: *Substrate-directed asymmetric reactions possible on substrate* **235**.

It was also reasoned that further diversity could be achieved by variation of the cleavage method (see Fig. 6.1c). The original concept involved the destruction of the β-hydroxyl moiety *via* a *retro*-aldol reaction to afford the chiral aldehyde. However, conventional nucleophilic side-chain cleavage could also be used to create a wide variety of carboxylic acid derivatives of use for natural product or drug discovery applications.

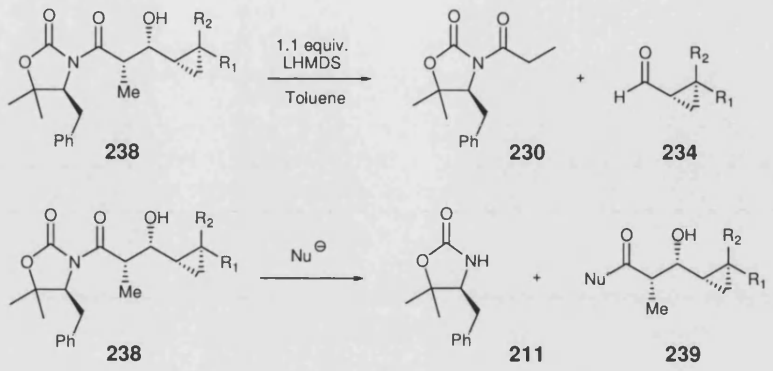


Fig 6.1c: *Alternative cleavage methods to remove chiral side-chain product.*

In this way, a wide variety of chiral products could be prepared as substrates for subsequent reactions which could introduce a variety of functional groups beyond those which would normally be accessible.

This chapter therefore describes further investigations into both the cyclopropanation and epoxidation reactions of these types of allylic alcohols, applies new synthetic strategies to the asymmetric synthesis of the cyclopropane-containing natural product Grenadamide and finally reports on preliminary investigations into the transfer of this methodology to polymer support.

6.2 Directed cyclopropanations

6.2.1 An efficient asymmetric synthesis of chiral cyclopropane-containing natural product – Grenadamide.

Grenadamide **240**, debromogrenadadiene **241** and grenadadiene **242** are natural products that were isolated from the marine cyanobacterium *Lyngbya majuscula,* by Sitachitta and Gerwick in 1998 [96] (see Figure 6.2.1a). These structurally unique cyclopropyl fatty acid derived metabolites were shown to demonstrate cannabinoid receptor binding activity, as well as cytotoxicity towards cancer cells. Baird and co-workers subsequently confirmed the absolute configuration of the cyclopropane fragment of grenadamide **240** as (*R*,*R*) *via* total

synthesis. Their synthesis required more than fifteen linear steps, with an enzymatic kinetic resolution being employed to introduce the stereogenic centres of the cyclopropane fragment.[97]

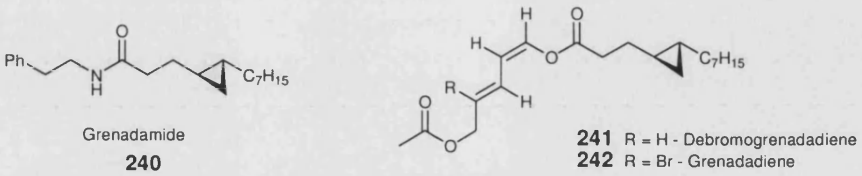
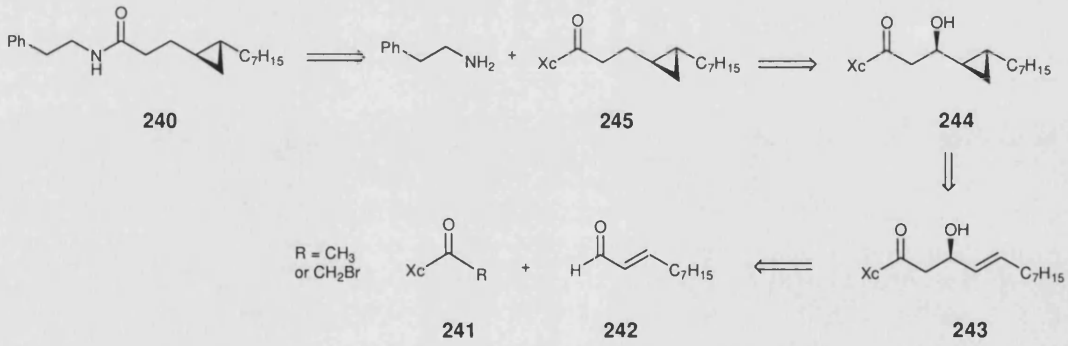


Fig 6.2.1a: *Structures of Grenadamide* **240**, *debromogrenadadiene* **241***and grenadadiene* **242**.

Retrosynthetic analysis.

A consideration of the structure of grenadamide highlighted the key chiral δ,γ-cyclopropane amide moiety that could be easily prepared by the 'temporary' stereocentre / substrate directed reaction strategy described above. An initial retrosynthesis showing the key structural components (see Scheme 6.2.1a) is described below. In this proposal, β-hydroxy alkene **243** could be prepared from the asymmetric reaction of chiral auxiliary **241** with α,β-unsaturated aldehyde **242**. This stereodefined hydroxyl group could then be used to direct a subsequent cyclopropanation reaction to form cyclopropane **244**. Removal of the hydroxyl functionality, followed by substitution of the chiral auxiliary fragment with the desired phenylethylamine fragment would afford grenadamide **240**.

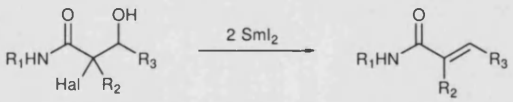


Scheme 6.2.1a: *Initial retrosynthesis for preparation of grenadamide* **240** *employing 'temporary' stereocentre / substrate directed reaction strategy.*

Analysis of this initial retrosynthesis revealed two key issues. Firstly, aldol reactions employing the boronates of *N*-acetyl-oxazolidin-2-ones were known to proceed with poor levels of diastereoselectivity, and hence the presence of substituents at the α-carbon is essential to achieve the aldol product in good yield. It is possible this issue could be circumvented by the use of a bromoacetyl-oxazolidin-2-one in a Reformatsky-type process since the resultant zinc enolates had been shown to proceed with high levels of diastereoselectivity in aldol reactions, albeit in often poor yields.

However, even if this issue of diastereoselectivity could be resolved, subsequent removal of the isolated β-hydroxyl group of **244** after cyclopropane formation would not be a trivial matter. Conventional methods for removing such a group generally rely on the formation of a carbocation or radical intermediate, however the presence of either of these features adjacent to a cyclopropane ring would lead to its destruction.

Therefore, it was proposed that the use of chloroacetyl-oxazolidin-2-one **246** would address both these issues. Firstly, the presence of an α-substituent would ensure high levels of diastereoselectivity in the initial aldol reaction. In addition, the presence of an α-chloro-substituent would facilitate cleavage of the β-hydroxy group *via* a β-elimination mechanism in which both the chloro- and hydroxyl- functionalities are removed in a single step, according to the method of Concellon *et al.*(see scheme 6.2.1b). [98]

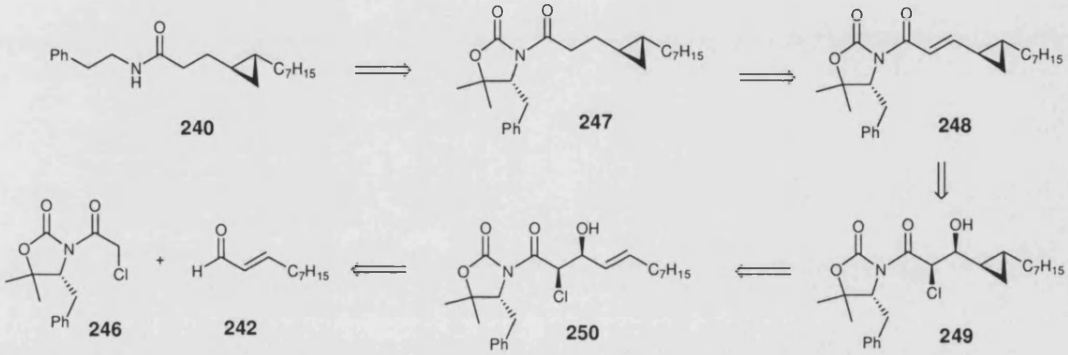


Scheme 6.2.1b: *Synthesis of (E)-α,β-unsaturated amides from β-hydroxyamides with SmI_2 as reported by Concellón.*

It was also decided to employ a SuperQuat auxiliary rather than a classic Evans-oxazolidin-2-one due to the more versatile cleavage profile of the former.[82] With the risk of endocyclic cleavage minimised by the use of a SuperQuat auxiliary, it was proposed that the chiral auxiliary fragment could be cleaved in good yield *via* direct aminolysis with phenylethylamine.

The refined retrosynthetic analysis is therefore shown in Scheme 6.2.1c. Grenadamide **240** would be prepared by direct aminolysis of the oxazolidin-2-one fragment of **247** using

phenylethylamine as a nucleophile. **247** would be prepared by reduction of α,β-unsaturated cyclopropane **248**, which could be derived from β-elimination of α-chloro-β-hydroxy-cyclopropane **249**. The cyclopropane ring of **249** could be introduced stereoselectively *via* a hydroxyl directed cyclopropanation reaction on *syn*-aldol **250** that would be prepared from aldol reaction of the (*Z*)-boron-enolate of *N*-chloroacetyl-5,5-dimethyl-oxazolidin-2-one **246** with (*E*)-dec-2-enal **242**.



Scheme 6.2.1c: *Refined retrosynthetic analysis of Grenadamide* **240**.

Synthesis of Grenadamide[*]

The first task was to employ the *syn*-aldol / directed cyclopropanation methodology described earlier (see Fig 6.1a) for the asymmetric synthesis of cyclopropane **249** in high de.

Therefore, (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **211** was first prepared in 72% yield from unnatural D-phenylalanine, according to the method of Bull *et al.* (Scheme 6.2.1d). [99] Hence D-phenylalanine underwent esterification with MeOH to protect the acid functionality with *N*-Boc protection of the amine to afford **252** in 94% yield. **252** was then treated with four equivalents of methyl magnesium bromide (MeMgBr) to introduce the gem dimethyl groups, forming **253** in 84% yield. Finally, base-promoted cyclisation of the alkoxide of **253** gave (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **211** in 90% yield after recrystallisation, corresponding to an overall 72% yield from D-phenylalanine.

[*] Part of this work was carried out in conjunction with final year project student Sarah Duffill and Matt Cheeseman.

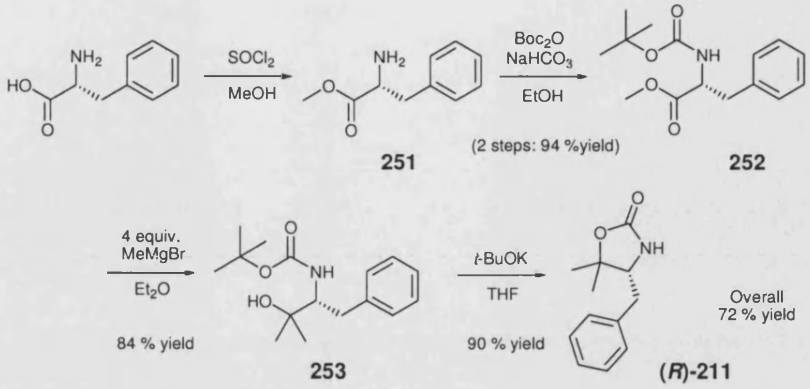
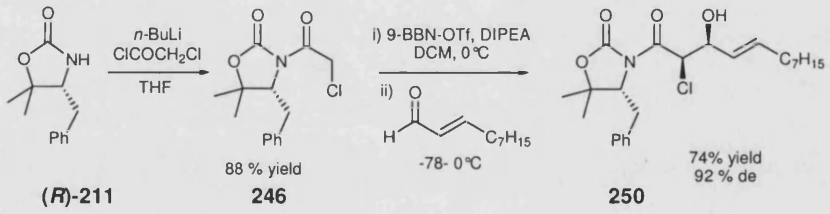


Fig 6.2.1d: *Synthesis of SuperQuat auxiliary* **211** *from unnatural (D)-phenylalanine, according to the method of Bull et al.*

Treatment of **(*R*)-211** in THF at –78 °C with 1.1 equivalents of *n*-BuLi, followed by addition of 1.1 equivalents of chloroacetyl chloride gave α-chloroacetyl-oxazolidin-2-one **246** in 78% yield after recrystallisation (see scheme 6.2.1e). **246** was then subjected to *syn*-aldol conditions developed within the SDB group,[95] modified from the method of Caddick *et al.*[63] Treatment of **246** with 1.1 equivalents of 9-BBN-OTf and $^{i}Pr_2NEt$ in CH_2Cl_2 at 0 °C, followed by cooling to –78 °C and addition of (*E*)-dec-2-enal resulted in *syn*-aldol **250** in 92% de, which was purified to >95% de in 74% yield following silica chromatography. The *syn*-stereochemistry of aldol **250** was confirmed from the small $J_{(2',3')}$ coupling constant of 3.5 Hz observed in the ^1H NMR spectrum.*

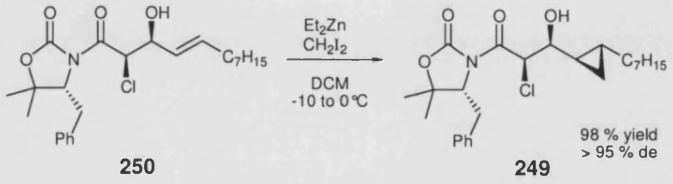


Scheme 6.2.1e: *Acylation of SuperQuat-oxazolidin-2-one auxiliary* **(*R*)-211**, *followed by diastereoselective aldol reaction to give syn-aldol* **250**.

Reaction of α-chloro-β-vinyl *syn*-aldol **250** with 5 equivalents of Et_2Zn and CH_2I_2 in CH_2Cl_2 at –10 °C, resulted in a highly stereoselective cyclopropanation reaction, to afford

* *anti*-α-alkyl-β-hydroxy-*N*-acyl-oxazolidin-2-ones normally exhibit $J_{(2',3')}$ coupling constants of ≥ 7.0 Hz, see reference (59) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392-393.

syn-cyclopropyl aldol **249** in >95% de and in 98% yield, see Scheme 6.2.1f. [100] Cyclopropanations under this type of modified Furukawa conditions are normally *syn*-selective (for reasons discussed below) and as a consequence the absolute configuration of **249** was assigned accordingly. In addition, the configuration of similar substrates has been confirmed by X-ray crystallography.



Scheme 6.2.1f: *Directed cyclopropanation of syn-aldol* **250** *under modified Furukawa conditions.*

The diastereoselectivity of this reaction is determined by minimisation of allylic strain in the transition state (see Scheme 6.2.1g). The carbenoid cyclopropanating species (formed from CH_2I_2 and Et_2Zn) coordinates to the stereodirecting hydroxyl group which then determines which of the diastereotopic faces of the olefin is cyclopropanated. For *trans*-allylic alcohol **254**, transition state **255a** is energetically favoured in comparison to transition state **255b** due to smaller $A^{1,3}$ strain resulting from the H-H interaction in **255a** compared to the R_1-H interaction in **255b**. The reactive conformation of the lower energy transition state **255a** therefore leads to formation of *syn*-cyclopropyl alcohol **256a** in high de.

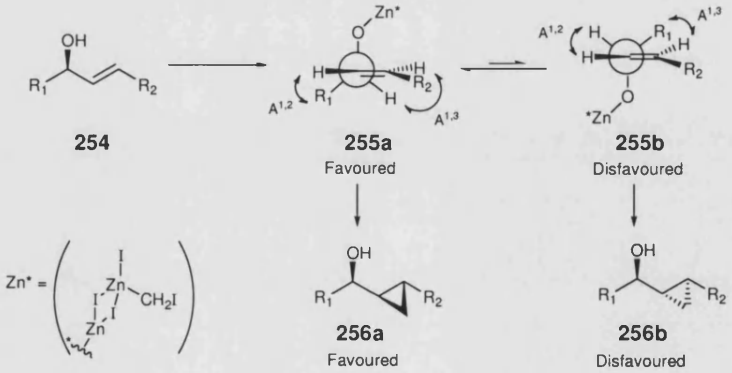
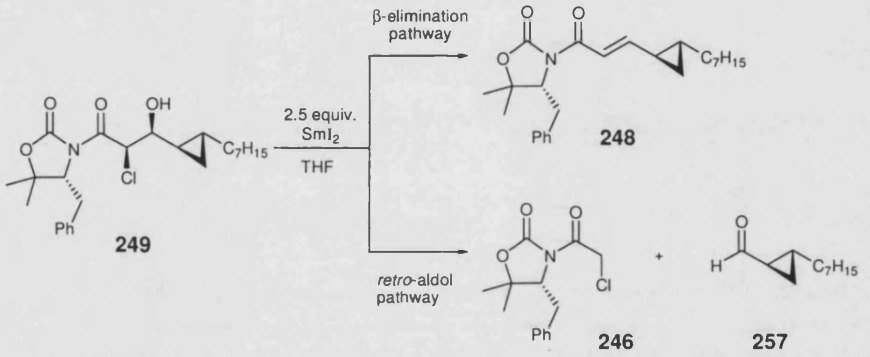


Fig 6.2.1g: *Minimisation of allylic strain in the cyclopropanation of* trans-*allylic alcohol* **254** *leads to* syn-*stereoselectivity.*

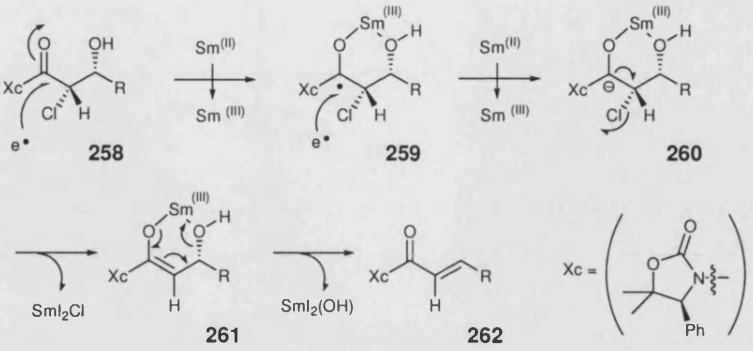
β-elimination

Attempts to perform β-elimination on **249** and thus simultaneously remove both the chloro- and hydroxyl- substituents, employed SmI_2, according to the method of Concellon.[98] Treatment of **249** with 2.5 equivalents of a solution of commercially available SmI_2 in THF at room temperature for 30 minutes afforded a mixture of products consisting of the desired α,β-unsaturated cyclopropane **248** (40%), starting material **249** (20%) and the two products of *retro*-aldol elimination, *N*-chloroacetyl-oxazolidin-2-one **246** (20%) and cyclopropyl-aldehyde **257** (20%) as shown in Scheme 6.2.1h.



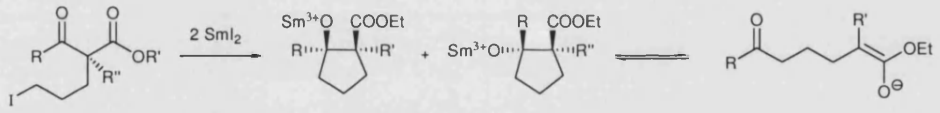
Scheme 6.2.1h: *Two possible reaction pathways in the attempted β-elimination reaction of* **249**, *one preparing the desired α,β-unsaturated cyclopropane* **248** *and the other involving an unwanted retro-aldol pathway to afford* **246** *and* **257**.

The mechanism for the samarium diiodide mediated β-elimination mechanism is not fully established but one possible mechanism is shown below in scheme 6.2.1j. Samarium (II) is oxidised to samarium (III) with the release of a single electron that reacts with the exocyclic carbonyl of **258** to afford radical anion intermediate **259**, which is then further reduced by another equivalent of samarium to form anionic intermediate **260**. Elimination of the α-chloro-substituent then affords samarium (III) enolate **261**. Finally, elimination of the β-hydroxyl group *via* a cyclic mechanism affords (*E*)-α,β-unsaturated-oxazolidin-2-one **262**. The chelated six-membered ring transition state is thought to be responsible for the high diastereoselectivity observed in this reaction.



Scheme 6.2.1j: *Proposed mechanism for SmI_2-mediated β-elimination reaction of α-chloro-β-hydroxyl-***258**

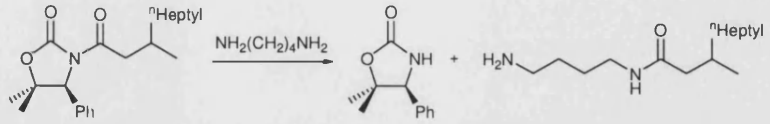
However, this mechanism does not account for the competing *retro*-aldol pathway observed in this reaction. Again, the mechanism of this step is not clear, but literature precedent suggests the retro-aldol pathway is likely to be mediated by the Sm(III) that is generated as a result of the elimination pathway, e.g. *retro*-aldol process observed by Molander *et al.* as shown in Scheme 6.2.1k. [101]



Scheme 6.2.1k: *Retro-aldol – aldol process results in equilibration of the initially formed aldol products as reported by Molander et. al.*

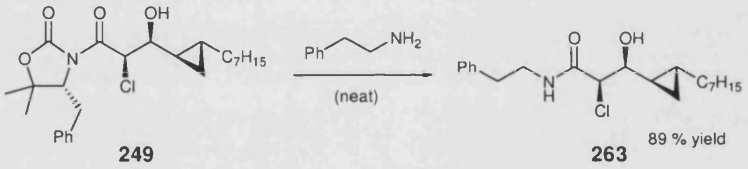
The occurrence of a *retro*-aldol reaction was not noted in Concellon's original work on the β-elimination reactions of simple amides, esters and ketone products. It was therefore proposed that the presence of the oxazolidin-2-one fragment in **249** must have been responsible for promoting this unique *retro*-aldol reaction pathway. It was reasoned that this issue could be circumvented be replacing the oxazolidin-2-one fragment with a simple amide, which would then hopefully undergo a clean β-elimination reaction.

It had previously been shown by Davies *et al.* that *N*-acyl-SuperQuat auxiliaries underwent clean aminolysis reactions with primary amines, see scheme 6.2.1m.[90]



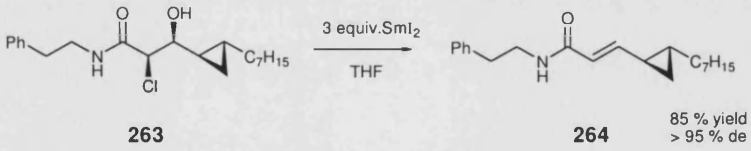
Scheme 6.2.1m: *Direct aminolysis of* N*-acyl-SuperQuat-oxazolidin-2-one, as reported by Davies et al.*

Hence α-chloro-cyclopropyl-*syn*-aldol **249** was dissolved in neat phenylethylamine and stirred overnight, which resulted in cleavage of the oxazolidin-2-one auxiliary to afford the desired α-chloro-cyclopropyl amide **263** as the only product in 89% yield after column chromatography, (see Scheme 6.2.1n). Fortunately, no competing side products from nucleophilic displacement of the α-chloro group by the amine or competing nucleophilic attack at the endocyclic carbonyl were observed in this reaction.



Scheme 6.2.1n: *Aminolysis of α-chloro-cyclopropyl-syn-aldol* **249** *with phenylethylamine.*

This new α-chloro-cyclopropyl amide **263** was then treated with samarium diiodide in THF to afford the desired vinylcyclopropane **264** in 85% yield and >95% de, with no competing products arising from the *retro*-aldol reaction being observed (see Scheme 6.2.1p)

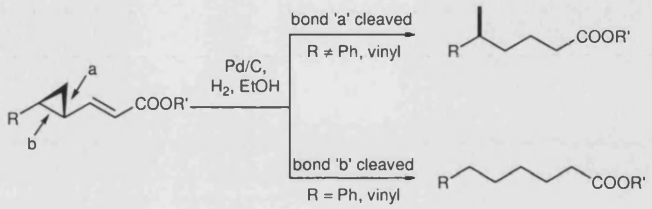


Scheme 6.2.1p: *Samarium diiodide mediated β-elimination reaction of α-chloro-cyclopropyl amide* **263.**

Reduction of double bond

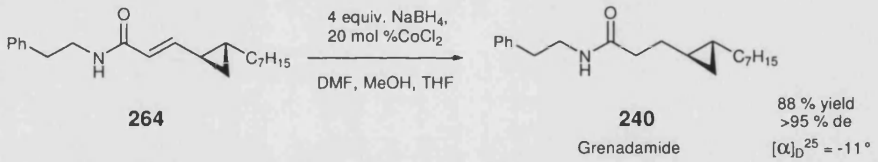
The final step of the synthesis of Grenadamide was the reduction of the alkene moiety. However, the need to reduce the double bond of vinylcyclopropane **264**, whilst leaving the adjacent cyclopropyl group intact, meant that catalytic hydrogenation methods could not be used. It is well established that transition metals such as palladium, rhodium, platinum and

mercury can promote cyclopropane ring opening reactions and Barrett *et al.* have demonstrated the regioselective ring opening of vinylcyclopropanes under catalytic hydrogenation conditions (Pd / C, EtOH) that were intended to cause hydrogenation of the double bond (see scheme 6.2.1q).[102]



Scheme 6.2.1q: *Regioselective ring opening of vinylcyclopropanes upon treatment with H_2 and Pd/C in EtOH.*

Therefore, an alternative method involving conjugate reduction of **264** with $NaBH_4$ and $CoCl_2$ was employed according to the method of He and Deng.[103] As depicted in Scheme 6.2.1r, vinylcyclopropyl amide **264** was treated with excess $NaBH_4$ with catalytic $CoCl_2$ in MeOH / DMF to afford grenadamide **240** in 88% yield and >95% de.



Scheme 6.2.1r: *Reduction of vinylcyclopropyl amide* **264** *with $NaBH_4$ and $CoCl_2$.*

The spectroscopic data of this sample of (*R,R*)-Grenadamide **240** matched that previously published for this natural product. The specific rotation of $[\alpha]_D^{lit} = -11$ ($[\alpha]_D^{25} = -11$) [97] confirmed the correct enantiomer of this natural product had been prepared. The asymmetric synthesis of Grenadamide **240** had therefore been completed in six steps and 42% overall yield from oxazolidin-2-one (***R*)-211**

6.3 *Directed epoxidations*

The most widely exploited substrate directable transformation to date has been the hydroxyl directed epoxidation of chiral allylic alcohols. A popular method of achieving this transformation is *via* the use of a vanadium catalyst, due to its significant rate enhancement effect. In the catalytic cycle described in Fig. 6.3.1a,[104] the lower-valent $VO(acac)_2$ complex is oxidised by *t*-BuOOH to afford a catalytically active d^0 vanadate ester which undergoes rapid ligand exchange to afford intermediate **267**. Bidentate coordination of the alkylperoxide activates intermediate **268**, with loss of a further alkoxide ligand. The alkene then initiates nucleophilic attack of the oxygen atom of **268** in the rate- and stereochemistry-determining step to afford epoxy alcohol complex **269**. Upon dissociation of the epoxy alcohol and *t*-BuOH side product, the active site on the vanadium centre is regenerated, thus completing the catalytic cycle.

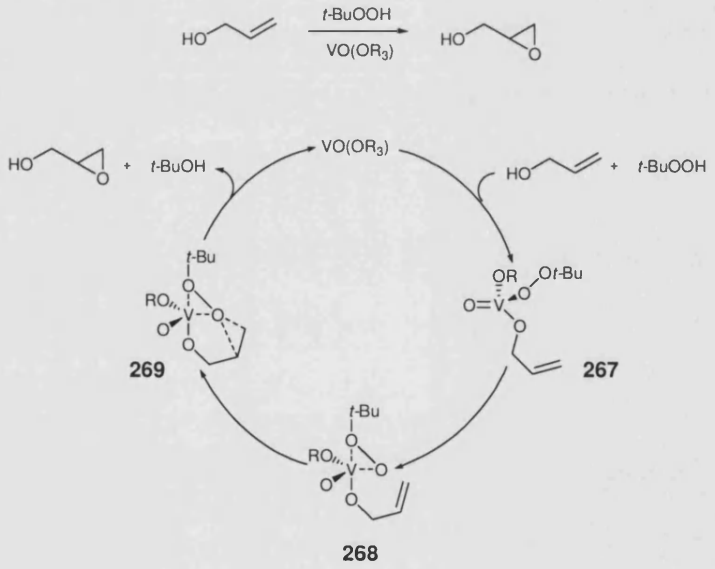
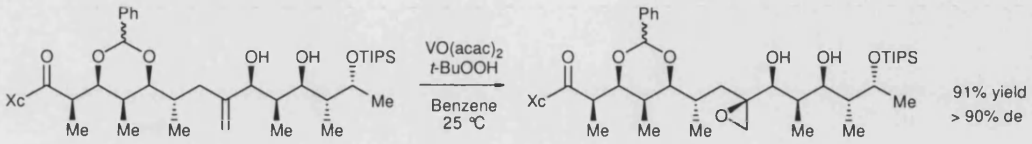


Fig 6.3.1a: *Proposed mechanism for the vanadium catalysed epoxidation of allylic alcohols.*

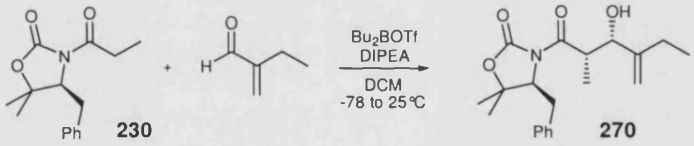
In cases where chiral allylic alcohols are employed, the diastereoselectivity of these types of allylic epoxidation reactions arises from minimisation of $A^{1,3}$-strain in the transition state, as previously discussed for directed cyclopropanation of allylic alcohols (see Section

6.2.1). Evans and co-workers have achieved good results employing this reaction for the synthesis of macrolide antibiotics (see scheme 6.3.1a). [105] In this example, excellent levels of diastereocontrol were achieved for the hydroxyl-directed epoxidation of a 1,1-disubstituted chiral allylic alcohol, despite the presence of many surrounding stereocentres that could potentially influence the stereocontrol of the reaction.



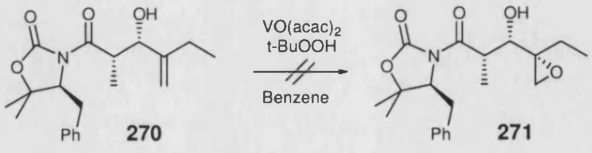
Scheme 6.3.1a: *Hydroxyl-directed epoxidation for the synthesis of macrolide antibiotics.*

Previous work within the SDB group had sought to test this hydroxyl-directed epoxidation reaction on our substrates, and hence 1,1-disubstituted unsaturated *syn*-aldol **270** was prepared. The boron enolate of (*S*)-*N*-propionyl-4-benzyl-oxazolidin-2-one **230** was treated with 2-ethylacrolein to afford *syn*-aldol **270** in 81% yield and >95% de (see Scheme 6.3.1b).



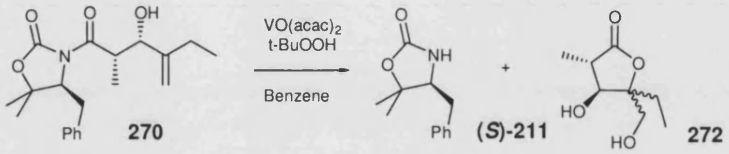
Scheme 6.3.1b: *Aldol reaction of solution phase N-propionyl oxazolidin-2-one* **230** *with 2-ethylacrolein to afford* syn-*aldol product* **270**.

270 was then treated with 10 mol% $VO(acac)_2$ and one equivalent of *tert*-butyl hydrogen peroxide in benzene at room temperature, followed by aqueous work-up (see Scheme 6.3.1c.) However, examination of the ^{1}H-NMR spectrum of the reaction product revealed no trace of the expected epoxy-aldol **271**, implying that it had not been formed under these reaction conditions.



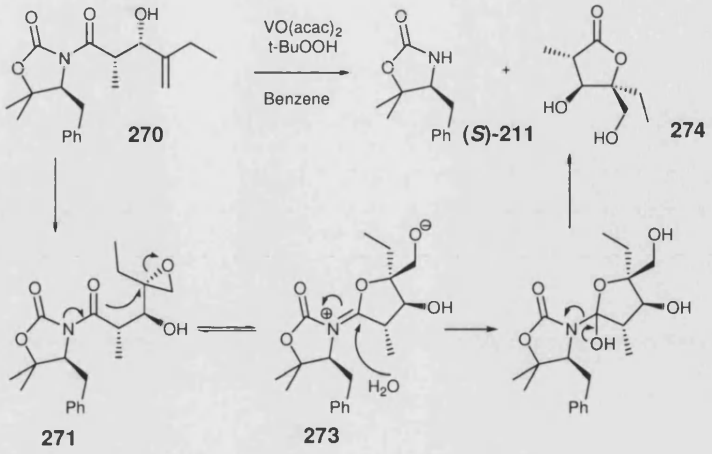
Scheme 6.3.1c: *Proposed epoxidation of syn-aldol* **270**, *however epoxy-aldol* **271** *was not formed.*

Instead the ^{1}H-NMR spectrum revealed only the presence of *N*-H oxazolidin-2-one **(*S*)-211**, with no products derived from the *syn*-aldol side-chain. However, subsequent saturation of the aqueous layer generated during work-up with sodium chloride, followed by back-extraction with ethyl acetate, resulted in isolation of lactone **272** in 78% yield and >95% de (see scheme 6.3.1d)



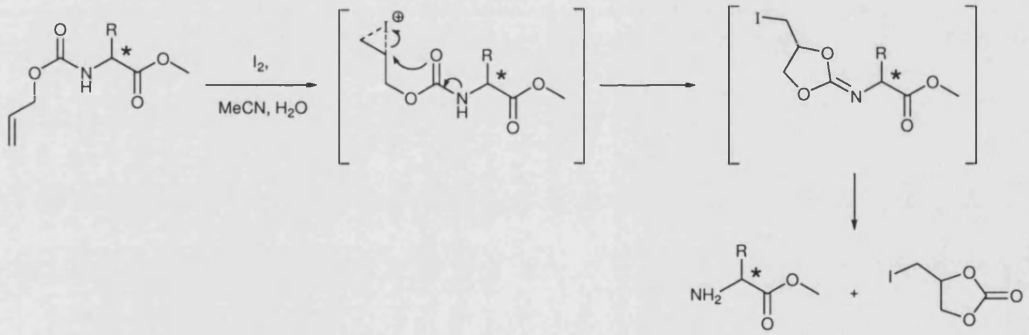
Scheme 6.3.1d: *Treatment of syn-aldol* **270** *according to standard directed epoxidation conditions leads to formation of N-H oxazolidin-2-one* **(*S*)-211** *and lactone* **272**.

Following this discovery, I sought to further investigate this useful, if not entirely unexpected, synthesis of chiral hydroxyl-*gamma*-lactones. The proposed mechanism for the formation of lactone **272** is shown in Scheme 6.3.1e. It is proposed that hydroxyl-directed epoxidation occurs on the 1,1-disubstituted alkene to afford the *syn*-epoxy-aldol **271**. The configuration of this step was assigned on the basis of literature precedent of similar 1,1-disubstituted alkenes as attempts to isolate the epoxy-aldol intermediate were not successful. It is then proposed that the exocyclic carbonyl of the side-chain, facilitated by the electron-donating effect of the adjacent nitrogen, acts as an intramolecular nucleophile to attack the epoxide and cause ring-opening with inversion of stereochemistry to form iminium intermediate **273**. Hydrolysis of the iminium intermediate, presumably upon aqueous work-up of the reaction, cleaved the oxazolidin-2-one fragment to generate lactone **274**.



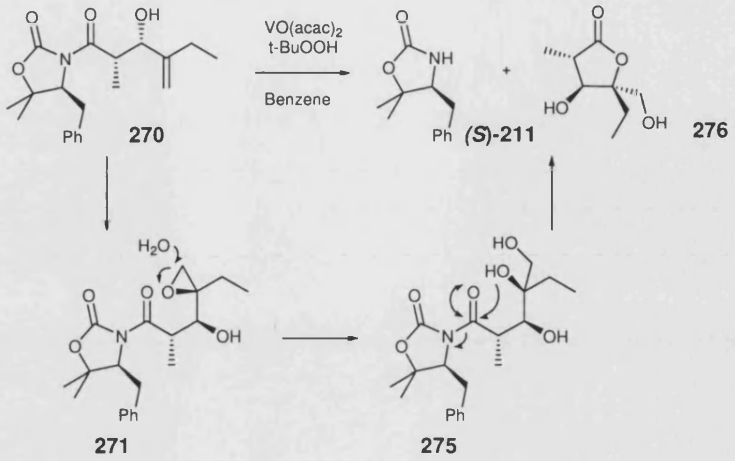
Scheme 6.3.1e: *Proposed mechanism for the intramolecular cyclisation of epoxy aldol to form lactone* **274.**

Based on the literature precedent, this intramolecular cyclisation pathway appeared to be the most likely mechanism. Miller *et al.* recently reported a mild, non-transition metal catalysed deprotection of *N*-allyloxycarbonyl amines using iodine in wet acetonitrile which was proposed to proceed *via* a similar mechanism (see scheme 6.3.1f).[106]



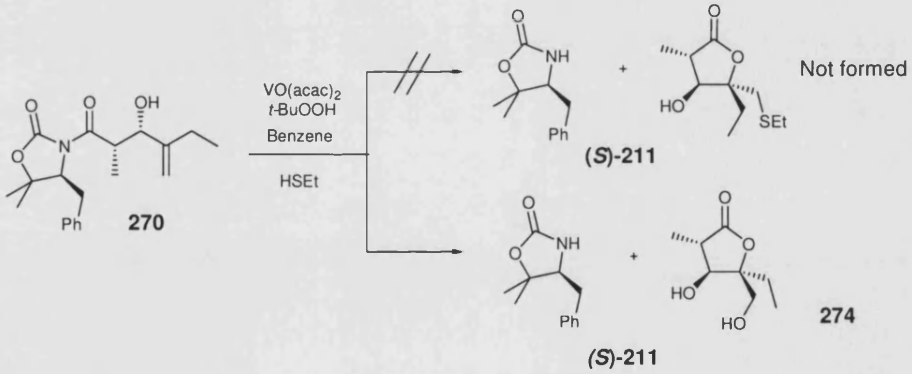
Scheme 6.3.1f: *Proposed mechanism of N-alloc deprotection via iodination / hydrolysis mechanism.*

However, there was also a possibility that direct hydrolysis of the intermediate epoxide with water could result in formation of a lactone product. In this pathway, water would attack the epoxide at the least sterically hindered end thus producing diol **275**, which would then cyclise *via* nucleophilic attack of the exocyclic carbonyl with the *N*-H-oxazolidin-2-one fragment being released as a stable leaving group (see scheme 6.3.1g)



Scheme 6.3.1g: *Alternative possible mechanism for lactone formation, resulting in gamma- lactone* **276**.

In an attempt to establish which of these two mechanisms was operating in this reaction, further experiments were conducted to investigate the possibility of an external nucleophile opening the epoxide. It was proposed that under strictly anhydrous conditions, repetition of this reaction with addition of an alternative nucleophile might result in incorporation of that nucleophile into the lactone product. Hence, *syn*-aldol **270** was treated with $VO(acac)_2$ and *t*-BuOOH in anhydrous benzene under strictly anhydrous conditions before addition of an excess of ethanethiol, see scheme 6.3.1h.

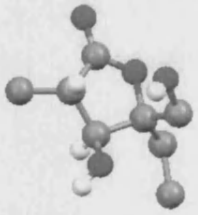


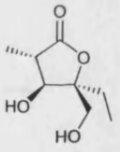
Scheme 6.3.1h: *Investigating the reaction mechanism: Addition of ethanethiol to the anhydrous reaction mixture does not result in its incorporation into the lactone product implying the mechanism does not proceed via opening of the epoxide with an external nucleophile.*

However, this reaction resulted in the original lactone **274** being formed with no sign of any products arising from incorporation of the thiol nucleophile. As ethanethiol is a better

nucleophile than water and would therefore be expected to undergo such a nucleophilic substitution reaction more readily, this result therefore implies that *gamma*-lactone formation does not proceed *via* opening of the intermediate epoxide by an external nucleophile.

It was also noted that the two possible mechanisms proposed above would result in the formation of lactones of opposite configuration at the quaternary centre. It was therefore reasoned that confirming the stereochemistry of the lactone product (as **274** or **276**) would help to confirm which of the two mechanisms was operating. It is notoriously difficult to assign the configuration of stereocentres within *gamma*-lactones *via* analysis of ^{1}H-NMR coupling constants,[107] so it was therefore necessary to obtain an X-ray crystal structure of the lactone **274** (see Figure 6.3.1b). This established the configuration of the quaternary centre of lactone **274** as (4*S*), thereby supporting the theory that the intramolecular ring opening mechanism proposed in Scheme 6.3.1e, involving nucleophilic attack on the epoxide by the exocyclic carbonyl, and resulting in ring-opening with inversion of stereochemistry at C-4.





274

Fig 6.3.1b: *X-ray crystal structure of lactone* **274** *confirming the stereochemistry of the C-4 quaternary centre as (S).*

To further investigate the scope of this reaction, further substrates were prepared *via* aldol condensation of *N*-propionyl-oxazolidin-2-one **230** with the corresponding aldehyde (according to Scheme 6.3.1b). All aldol products were achieved in good yield and >95% de after column chromatography, see Table 6.3.1a.

These substrates were then subjected to the epoxidation conditions described earlier and reacted for 2-4 hr at rt, followed by aqueous quench. The resulting lactones were often

found to be water-soluble, so were generally obtained by saturation of the aqueous layer and back-extraction into ethyl acetate. In all cases, there was some indication of the reaction occurring, although it was not always possible to isolate the lactone product in pure form.

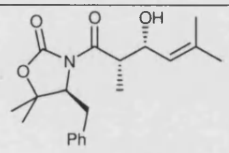
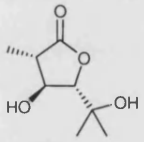
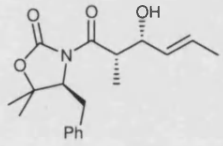
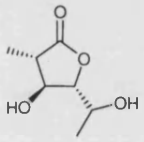
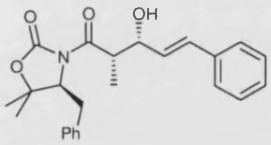
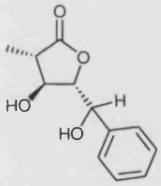
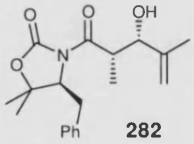
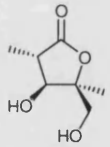
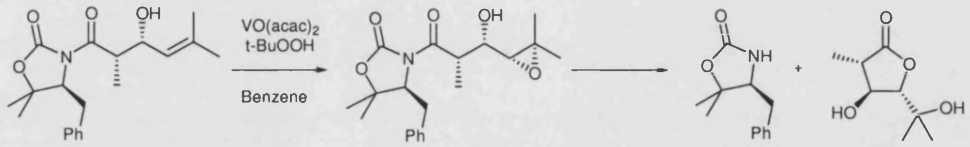
syn-aldol substrate	Yield of *syn*-aldol substrate [a] (%)	Lactone product	Yield [b] (%) / de [c] (%)
 **277**	90	 **278**	75% yield [d] > 95% de [e]
 **279**	93	 **280**	38% yield [b] > 95% de
 **281**	88		Only NH aux isolated, plus complex mixture of products
 **282**	89	 **283**	70% yield [e] > 95% de [e]

Table 6.3.1a: *Epoxidation / cyclisation reaction with alternative aldehydes to produce N-H oxazolidin-2-one* **(*S*)-211** *and lactones* **278, 280** and **283.** *Reaction conditions: 10mol% VO(acac)$_2$, 1 equiv. t-BuOOH, benzene, 2 hrs, rt.* [a] *Isolated yield after column chromatography of the crude product. All aldols had de >95% according to analysis of their respective ^{1}H-NMR spectra* [b] *Isolated yield after column chromatography.* [c] *de determined by ^{1}H-NMR.* [d] *Yield after reaction conducted for 12 hours at room temperature to ensure all epoxide converted to lactone.* [e] *After recrystallisation.*

Treatment of *syn*-aldol **277** with VO(acac)$_2$ and *t*-BuOOH, under the same conditions developed previously did not result in the direct formation of the lactone product **278** (see Scheme 6.3.1j). Instead a compound that was structurally similar to the starting aldol was recovered, which spectroscopic analysis revealed to be the epoxide intermediate **284**. The stereochemistry of this epoxide was inferred from literature precedent and by minimisation

of allylic strain in the transition state. Although stable for long enough to be characterised, epoxide **284** was found to decompose over a couple of days forming *N*-H oxazolidin-2-one (*S*)-**211** and lactone **278**. However, extending the duration of the epoxidation reaction to 12 hours resulted in complete conversion to lactone **278** and *N*-H-oxazolidin-2-one (*S*)-**211** with no trace of epoxide **284**. The epoxide intermediates were not isolated in any of the other examples attempted and it is not entirely clear why this epoxide was more stable than any of the others, although it may be that the formation of the more hindered tertiary alcohol product is less favoured.



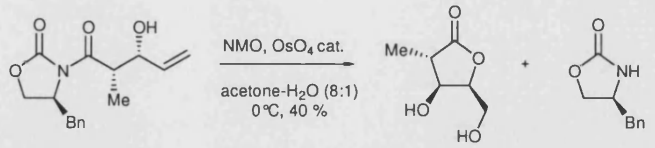
277 284 (*S*)-211 278

Scheme 6.3.1j: *Epoxidation of syn-aldol* **277** *to form epoxide* **284**, *with subsequent cyclisation to form N-H oxazolidin-2-one* (*S*)-**211** *and lactone* **278**.

The reaction with *trans*-cinnamaldehyde-derived aldol **281** did yield *N*-H oxazolidin-2-one (*S*)-**211** but also afforded a complex mixture of products in which the lactone could not be identified. This may be due to competing side reactions being possible due to the potential of this substrate to form a benzylic carbocation which could result in formation of competing products.

In summary, four lactones were prepared and isolated successfully, and in reasonable yield and high de. These lactones represent versatile chiral building blocks for further structural elucidation with three contiguous stereocentres having been easily formed in high de.

Recently, Dias *et al.* reported a similar route to diastereomeric γ-butyrolactone products *via* dihydroxylation of similar β-hydroxy-*N*-acyl-oxazolidin-2-one allylic alcohols, (see Scheme 6.3.1k).[108]



Scheme 6.3.1k: *Synthesis of γ-butyrolactone via dihydroxylation / lactonisation sequence.*

However, further investigations by members of the SDB group have revealed inconsistencies between the spectral data of similar lactones prepared by the two groups, implying a possible mis-assignment of the lactone's configuration. Further investigation into this issue is ongoing.

6.4 Application of methodology to solid phase.

Following the successful synthesis of a chiral cyclopropane containing natural product and some promising results towards the preparation of chiral *gamma*-hydroxy lactones in solution phase, the application of this strategy to a solid-phase system was investigated. Despite a number of examples of solid-supported asymmetric reactions in the literature, it is rare to find examples in which two consecutive asymmetric reactions have been conducted 'on-bead'. It was proposed that this strategy would greatly expand the scope of the applications of solid-supported chiral oxazolidin-2-one-type auxiliaries and allow a greater variety of chiral products to be formed.

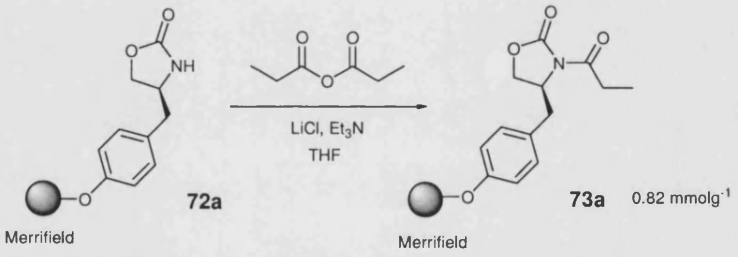
As in the solution phase strategy, the first stage was construction of the stereodefined hydroxyl group which would later act to direct a second asymmetric reaction. It was therefore necessary to develop conditions for an efficient asymmetric solid-supported aldol reaction. It was anticipated that development of optimal conditions for a solid-supported aldol reaction would not represent as much of a challenge as for the solid-supported enolate alkylation reactions previously considered. Earlier studies investigating solution phase aldol reactions had revealed no signs of any unwanted by-products from the aldol reaction, a feature which, if also applicable to solid phase versions, would hopefully lead to high yields of the desired aldol product in high purity. In addition, two separate reports of asymmetric

aldol reactions on solid-supported oxazolidin-2-one auxiliaries have previously been reported with aldol products of high de (90 – 98%) prepared.[31,32]

6.4.1 Optimisation of solid-phase asymmetric aldol reaction conditions.

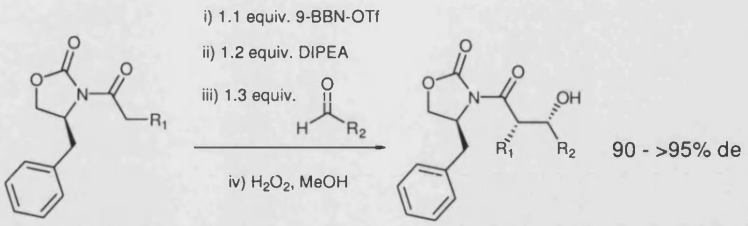
The first step in developing an efficient asymmetric solid-phase aldol reaction was selection of the appropriate polymer support. Unfortunately, the use of 9-BBN-OTf or Bu_2BOTf as a reagent for the aldol reaction ruled out the use of a 2-chlorotrityl-chloride resin-supported chiral auxiliary as the chlorotrityl linker was not stable to the Lewis acidic reaction conditions. It was therefore necessary to employ the more robust Merrifield-supported oxazolidin-2-one **72a**, however, as previously discussed, the use of this resin limited the extent of intermediate characterisation possible.

Merrifield supported oxazolidin-2-one **72a** was *N*-acylated with propionic anhydride under the standard reaction conditions optimised previously and described in Chapter 2.3, see scheme 6.4.1a. The approximate loading was determined as 0.82 $mmolg^{-1}$ by gravimetric analysis of the functionalised resin.



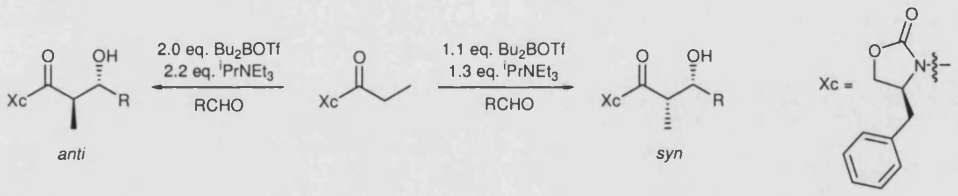
Scheme 6.4.1a: *N-acylation of Merrifield-supported N-H oxazolidin-2-one* **72a** *with propionic anhydride.*

The optimised conditions for solution phase *syn*-aldol reactions developed within the SDB group were described previously in Chapter 2.5, see Scheme 6.4.1b for brief details.



Scheme 6.4.1b: *Aldol reaction of solution phase N-acyl oxazolidin-2-one with an aldehyde.*

It had been noted that under these conditions, the reaction did not always proceed to completion, with the extent of the reaction appearing to be dependant on the quality of the boron reagent. It was therefore reasoned that the situation in the analogous solid phase reaction was likely to be worse, and due to the heterogenous nature of the system the reaction could be even less prone to proceeding to completion. A frequently cited advantage of solid phase synthesis is the option to use an excess of reagents to drive a sluggish reaction to completion with facile removal of the excess reagent from the product by simply filtering off the functionalised resin. This approach was therefore an obvious consideration in this example, where the presence of any starting material at the end of the reaction would result in contaminated products. However, Heathcock *et al.* had noted that the presence of excess Bu_2BOTf in some *syn*-aldol reactions (including those involving aromatic aldehydes) resulted in a reversal of diastereoselectivity with *anti*-aldols being formed [33](see scheme 6.4.1c). The authors proposed that this was due to the formation of different aggregation states depending on the number of equivalents of the boron reagent used and the nature of the base employed.

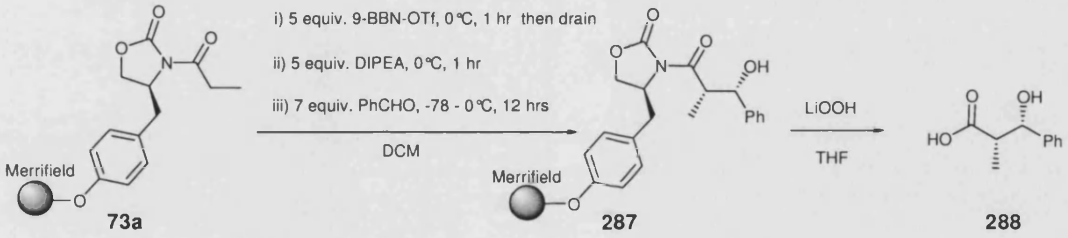


Scheme 6.4.1c: *Syn products formed when slight excess of boron reagent present, but with two-fold excess of born reagent, anti product formed. Selectivity highest when R contains aryl or S.*

However, this issue had previously been addressed on solid-phase by Phoon and Abell,[32] who had shown that an excess of boron reagent could be employed if the excess boron reagent was then drained away and the reaction solution replaced with fresh solvent. A

similar strategy had been successfully employed in my previous work with solid-supported enolate alkylation reactions where an excess of LHMDS was required to force the reaction to completion.

Therefore, *N*-propionyl oxazolidin-2-one resin **73a** in an IRORI Kan, suspended in DCM at 0 °C was treated with 5 equivalents of 9-BBN-OTf for 1 hour, after which time the reaction solution was removed *via* cannula. After the addition of fresh, pre-chilled DCM, 5 equivalents of DIPEA was added and the reaction stirred for a further hour. The entire reaction was then cooled to -78 °C before addition of 7 equivalents of benzaldehyde. The reaction was then allowed to warm to room temperature slowly and stirred for a further 12 hours, see Scheme 6.4.1d.



Scheme 6.4.1d: *Solid phase syn-aldol reaction of Merrifield-supported N-propionyl-oxazolidin-2-one* **73a** *with benzaldehyde, followed by LiOOH side chain cleavage to form syn-aldol acid* **288**.

Subsequent cleavage of the washed, dried resin with LiOOH, according to the procedure described earlier in Chapter 3.4.2b. resulted in cleavage of *syn*-aldol acid **288** in 58% yield*, 90% de and excellent purity (see Fig. 6.4.1a). The relative stereochemistry of the aldol product was assigned by the small $J_{(2,3)}$ coupling constant of 4.0 Hz.

* Yield based upon estimated original loading of auxiliary onto Merrifield resin, hence represents yield over three steps *i.e.* *N*-acylation, aldol reaction and finally LiOOH cleavage (with aqueous extraction).

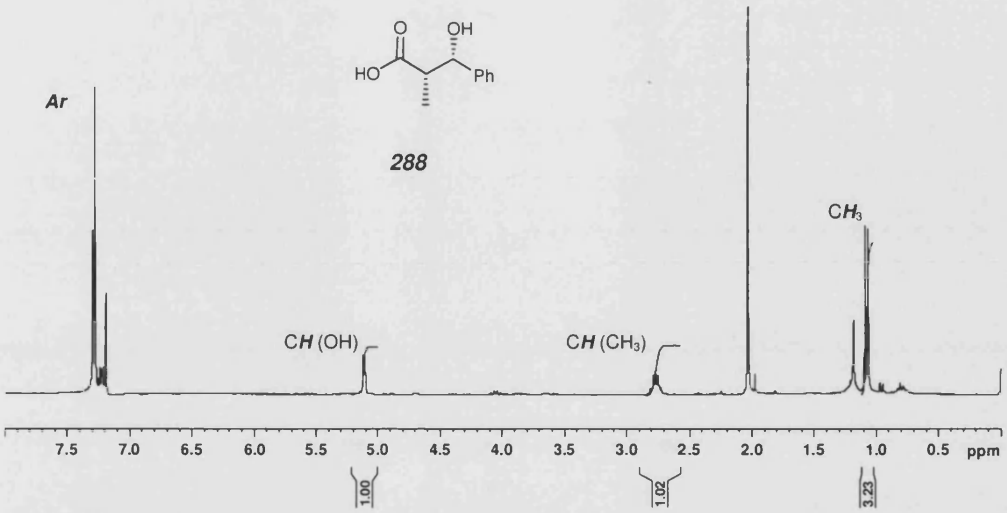


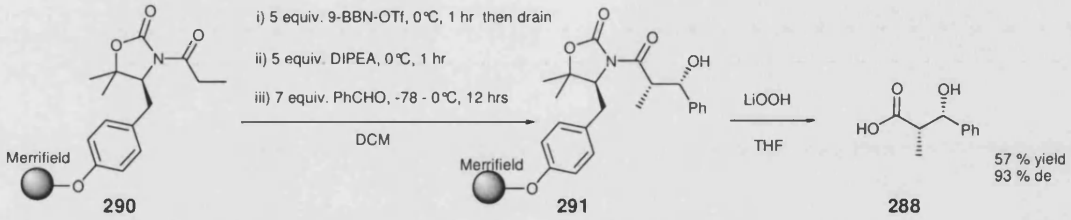
Fig. 6.4.1a: *^{1}H-NMR of* syn-*aldol acid* **288** *prepared via* syn-*aldol reaction of polymer supported N-propionyl oxazolidin-2-one* **73a** *with benzaldehyde, followed by LiOOH-mediated side-chain cleavage.*

Further experiments were conducted including varying the temperature of the reaction and varying the duration of treatment of the resin with each reagent. However no significant improvements to either the yield or the de of the *syn*-aldol-acid product were observed.

Both the de and the yield of this reaction were slightly lower than those achieved in the corresponding solution phase reaction. However, these results are comparable to those previously reported for solid phase systems of this type [31,32] and still result in formation of chiral products with good levels of stereocontrol. The reduced yield is disappointing, however it must be noted that the yield stated was calculated based on the estimated loading of the auxiliary fragment onto Merrifield resin so encompasses three separate reactions, *N*-acylation, an asymmetric aldol reaction and finally LiOOH cleavage (with aqueous extraction). The main losses in yield are thought to be due to the aldol reaction not being driven to completion despite the presence of excess reagents, and incomplete recovery of the acid product in the final acidic aqueous extraction.

Polymer-supported SuperQuat auxiliary **289** was also tested in this solid-phase aldol reaction. Hence Merrifield-supported *N*-propionyl SuperQuat oxazolidin-2-one **290** was treated with 9-BBN-OTf, diisopropylethylamine and benzaldehyde according to the method

described above (see scheme 6.4.1e). Subsequent LiOOH cleavage of the polymer-bound product afforded *syn*-aldol acid **288** in 57% yield and 93% de, an essentially identical result to that obtained using the polymer-supported Evans oxazolidin-2-one.



Scheme 6.4.1e: *Solid phase syn-aldol reaction of Merrifield-supported N-propionyl-5,5-dimethyl-oxazolidin-2-one* **290** *with benzaldehyde, followed by LiOOH side chain cleavage to form syn-aldol acid* **288**.

It was then decided to investigate alternative aldehydes in this reaction. The procedure detailed above was repeated using Evans' *N*-propionyl-oxazolidin-2-one **73a** with isobutyraldehyde, cyclohexanecarboxaldehyde and octyl aldehyde in turn, see Table 6.4.1a.

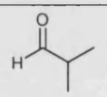
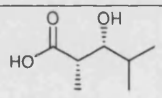
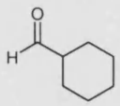
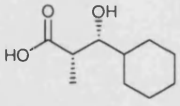
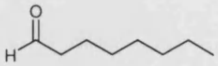
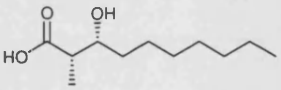
Aldehyde	Acid Product	Yield (%), de (%)
	 **289**	63% yield 90% de
	 **290**	66% yield >95% de
	 **291**	50% yield 90% de

Table 6.4.1a: *Solid phase aldol reactions employing alternative aldehydes.*

These results suggest that the reaction conditions optimised for the aldol reaction of **73a** with benzaldehyde were broadly applicable to other aldehydes. Reaction of **73a** with isobutyraldehyde, another commonly used aldehyde for optimising new aldol reaction conditions, resulted in similar results to those achieved with benzaldehyde. Superior results were achieved with the bulkier aldehyde cyclohexanecarboxaldehyde with no sign of the *anti*-diastereomer detectable in the ^{1}H-NMR spectrum. Perhaps unsurprisingly, the reaction employing octyl aldehyde resulted in a lower yield of *syn*-aldol acid (50%), albeit in a

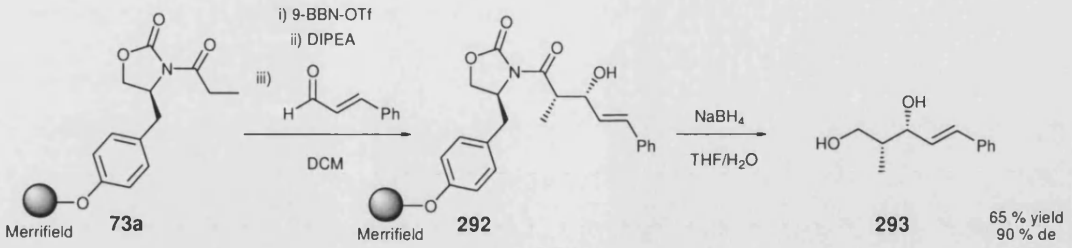
respectable 90% de. This is likely to be due to the aldol reaction itself being sluggish due to the less reactive long chain aldehyde and is a feature also seen in solution phase aldol reactions of this type.

Further optimisation of the solid-phase asymmetric aldol reaction conditions for each individual aldehyde would of course be possible and it is likely that higher yields could be gained. However, time restraints did not allow for further optimisation and therefore the current conditions for the solid-phase asymmetric aldol reaction were carried through to the next stage of research into a second, substrate-directed asymmetric reaction on the polymer-bound substrate.

6.4.2 Solid phase asymmetric aldol / directed cyclopropanation strategy

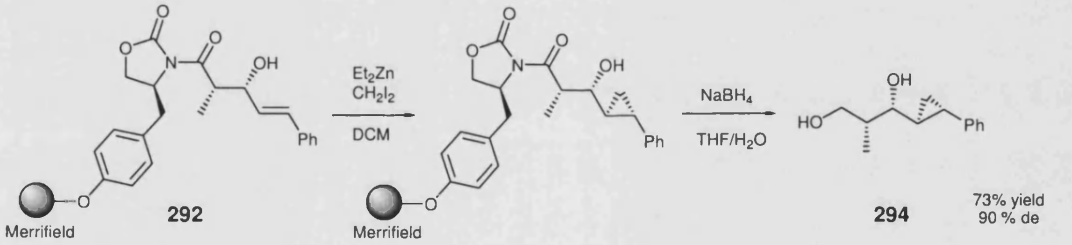
With conditions for a polymer-supported asymmetric aldol reaction in hand, preliminary investigations into the second asymmetric reaction were commenced. Following the success in solution phase of this strategy for the synthesis of the natural product Grenadamide, solid-phase directed cyclopropanations were initially investigated.

Firstly, it was necessary to prepare an appropriate polymer-supported *syn*-aldol product. Although previous solution phase studies towards the synthesis of Grenadamide had employed the long chain aldehyde *trans*-2 decenal, it was decided to use a simpler, more reactive aldehyde for these preliminary solid-phase reactions. Hence, the boron enolate of polymer-supported *N*-propionyl oxazolidin-2-one **73a** was treated with *trans*-cinnamaldehyde to form *syn*-aldol **292** according to the reaction conditions developed in Section 6.4.1, (see Scheme 6.4.2a). Subsequent side-chain cleavage employing $NaBH_4$ afforded *syn*-aldol alcohol **293** in 65% yield and 90% de.



Scheme 6.4.2a: *Solid phase syn-aldol reaction of Merrifield-supported N-propionyl-oxazolidin-2-one* **73a** *with trans-cinnamaldehyde, followed by $NaBH_4$ side chain cleavage to form syn-aldol alcohol* **293**.

Confident that the *syn*-aldol reaction had proceeded with good diastereoselectivity, the second asymmetric reaction was performed on functionalised resin **292**. In a similar procedure to that employed in solution phase, polymer-supported *syn*-aldol **292** was suspended in dry DCM at -10 °C and five equivalents each of diethylzinc and diiodomethane added. The reaction was then agitated for two hours, whilst allowing it to warm to 0 °C. Subsequent $NaBH_4$ cleavage of the thoroughly washed resin afforded *syn*-cyclopropane-alcohol **294** in approximately 90% de and 73% yield (after column chromatography) (see Scheme 6.4.2b). A trace of alkene starting material was also observed in the crude reaction product implying the reaction had not proceeded entirely to completion.



Scheme 6.4.2b: *Directed cyclopropanation of polymer-supported vinyl-syn-aldol* **292** *with subsequent $NaBH_4$ cleavage to form syn-cyclopropane-alcohol* **294**.

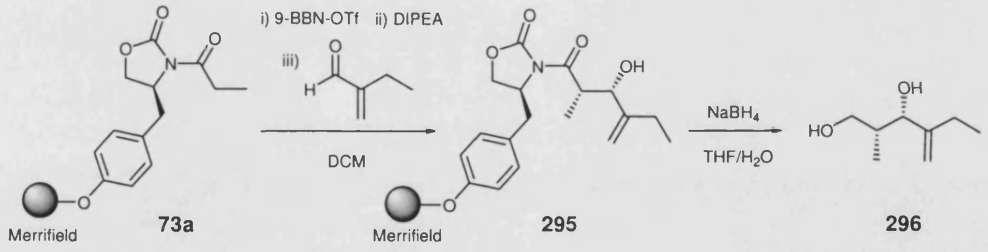
This reaction provided proof that the concept of a solid-supported asymmetric aldol / directed cyclopropanation reaction was not only possible, but could proceed in high diastereoselectivity and moderate yields (47% over two steps). Further work is required to investigate this reaction further, firstly aiming to improve the yield of the reaction considerably and later to explore the scope and limitations of these reactions.

6.4.3 Solid phase asymmetric aldol / directed epoxidation/lactonisation strategy

Following on from the successful solid phase directed cyclopropanation reaction, preliminary studies into a polymer-supported directed epoxidation/lactonisation reaction were conducted.

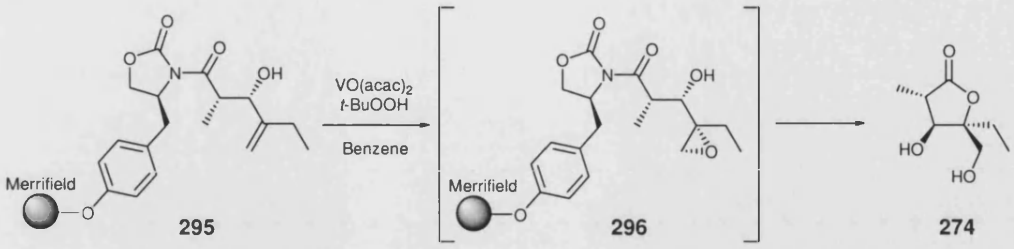
A significant feature of this reaction on solid phase is that cyclisation/lactonisation of the side chain would result in self cleavage of the lactone product from the polymer-supported oxazolidin-2-one. Whilst this is in some ways desirable as it eliminates the need for a separate cleavage step, it could also prove problematic since uncontrolled self-cleavage at inopportune times would lead to contamination of the lactone product with the reagents present in the reaction solution, thus negating the purification benefits of the solid-phase system.

Once again, the first step was synthesis of the appropriate polymer-supported *syn*-aldol substrate. The boron enolate of polymer-supported *N*-propionyl oxazolidin-2-one **73a** was treated with 2-ethylacrolein to form *syn*-aldol **295** according to the reaction conditions developed in Section 6.4.1, (see Scheme 6.4.3a). Subsequent side-chain cleavage employing $NaBH_4$ afforded *syn*-aldol alcohol **296** in 62% yield and ≥ 95% de.



Scheme 6.4.3a: *Solid phase syn-aldol reaction of Merrifield-supported N-propionyl-oxazolidin-2-one* **73a** *with 2-ethylacrolein, followed by* $NaBH_4$ *side chain cleavage to form syn-aldol alcohol* **296**.

Functionalised resin **295** suspended in benzene was then treated with an excess of $VO(acac)_2$ and *t*-BuOOH in a variation of the solution phase method described in Section 6.3.1, (see Scheme 6.4.3b)



Scheme 6.4.3b: *Directed epoxidation of polymer-supported vinyl-*syn*-aldol* **295** *followed by cyclisation / lactonisation to afford lactone* **274** *in solution phase and polymer supported N-H oxazolidin-2-one* **295**.

In solution phase it had been found that the cyclisation / lactonisation step appeared to occur spontaneously after epoxidation, with no sign of any epoxide remaining even after just 30 minutes. It was unclear whether or not this would also occur on solid phase, but to ensure the lactone product was recovered, the filtrate and washings of the resin were collected and evaporated. In order to remove the excess of vanadium, the residue was redissolved in DCM and passed through a plug of silica. Analysis of the resulting colourless oil revealed the presence of lactone **274** albeit in a moderate 58% yield and in 90% de. This result clearly shows that the concept of polymer-supported substrate-directable reactions is viable with some lactone **274** being prepared in high de. It is unfortunate that the self-cleavage step in this case resulted in the product being released into the reaction mixture thus complicating the purification procedure. It must be noted however, that this still represents an improvement when compared to the corresponding solution phase reaction where the lactone has to be separated not only from the excess vanadium but also from the *N*-H-oxazolidin-2-one which often has a similar R_f value. It is anticipated that other substrates might allow a more practical experimental procedure since in solution phase it was found that some substrates afforded an intermediate epoxide that was stable and could be isolated. If this could be repeated on solid-phase systems, then it might allow the removal of the excess vanadium before intramolecular cyclisation and self-cleavage of the lactone from the polymer occurs, thus simplifying the work-up procedure. Furthermore, it is anticipated that with further optimisation of both this reaction and the preceding aldol reaction, and a greater understanding of the epoxidation / lactonisation mechanism, improvements to the overall yield could be achieved. Unfortunately time restraints prevented further investigation into this area.

6.5 Conclusions

This chapter has described early attempts to develop new strategies for the use of Evans oxazolidin-2-one type chiral auxiliaries, both in solution and solid phase. The overall strategy involves the use of a chiral oxazolidin-2-one to induce chirality in an asymmetric reaction in a conventional manner. The newly formed chiral centre is then used to induce chirality to a second asymmetric reaction. The oxazolidin-2-one fragment is thus used indirectly to induce chirality at a site remote to its normal area of influence and hence the variety of enantiopure chiral products that can be formed from oxazolidin-2-one chemistry is greatly increased.

This strategy was demonstrated in the synthesis of the chiral cyclopropane-containing natural product Grenadamide. In this case, an asymmetric *syn*-aldol reaction was used to introduce a temporary stereogenic hydroxyl group, which was used to direct a substrate-directed cyclopropanation reaction. Further manipulations afforded the natural product in good yield and excellent de.

A variation of this strategy involving substrate-directed epoxidation of a chiral allylic alcohol was also investigated where it was found that an intermediate epoxide species was unstable and underwent self-cleavage to form the parent *N*-H oxazolidin-2-one and a chiral lactone in high de.

Attempts to apply these strategies to polymer-supported systems were promising. Firstly, conditions for a polymer-supported asymmetric *syn*-aldol reaction were developed to allow the formation of a *syn*-aldol substrate with a stereodefined hydroxyl group, in high de. Subsequent attempts to perform substrate-directed cyclopropanations and epoxidation / lactonisation reactions were successful, with products of good de being obtained albeit in moderate yields. Unfortunately, time restraints prevented further optimisation of these systems, but it is anticipated that further investigation would allow the overall yields of the chiral products to be increased thus affording practical solid-phase systems for the asymmetric synthesis of libraries of chiral products.

Chapter 7 Synthetic procedure and spectroscopic data

7.1 General Experimental

All solvents were either distilled before use and stored in the presence of 3Å molecular sieves (tetrahydrofuran and diethyl ether were distilled from sodium wire, acetonitrile, dichloromethane and DMF were distilled from calcium hydride) or obtained from an MBraun solvent purification system. Methanol was obtained in anhydrous form from Fluka. All commercial reagents were used without purification unless stated otherwise.

TLC using aluminium backed plates precoated with Macherey-Nagel Sil G, monitored all reactions. Visualisation of these plates was by 254 nm UV light and/or $KMnO_4$, PMA or vanillin dips followed by gentle warming.

Flash chromatography was carried out using Davisil LC 60A silica gel (35-70 micron) purchased from Flurochem. Samples were either pre-absorbed onto silica or loaded as saturated solutions in an appropriate solvent.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker 300MHz spectrometer. Chemical shifts are quoted in parts per million and are referenced to the residual solvent peak or to $SiMe_4$ (δ = 0.00 ppm) as an internal standard. Coupling constants (J) are given in Hz to the nearest 0.5 Hz and multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), unresolved multiplet (m) or broad (br.). All structural assignments of both proton and carbon spectra were achieved with the aid of COSY, HMQC, HMBC and PENDANT experiments wherever possible and with comparisons from analogous literature compounds. In all ^1H-NMR spectra, the aromatic protons derived from the original tyrosine molecule (*i.e.* C_6H_4 moiety) represent an AA'BB' system due to magnetic inequivalence. The signals are thus described as apparent doublets (app. d) although in reality this is a significant simplification.

IR spectra were recorded from thin films or KBR disc on a Perkin-Elmer 1600 series FT-IR spectrophotometer in the range 600-4000 cm^{-1}, with internal calibration. Selected absorbances are quoted as υ in cm^{-1}.

Mass spectra, including high-resolution spectra, were run by the EPSRC mass spectrometry service, Swansea. Electron impact (EI) and chemical ionisation (CI) analyses were performed in positive ionisation mode.

Elemental analyses were performed with an Exeter analytical, INC. CE-440 elemental analyser in the Chemistry Department of the University of Bath.

Melting points were measured on a Büchi 535 series instrument and are uncorrected.

Optical rotations were performed on an Optical Activity LTD: AA-10 automatic polarimeter.

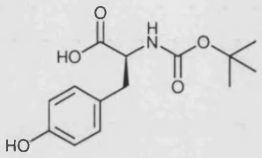
High pressure liquid chromatography was carried out using a TSP Thermo Separation products spectra SERIES and Spectra Physics Systems using Chiralcel OD®, AD® and OJ® columns obtained from Fisher Scientific Supplies.

Diastereomeric excess (de) values were determined by ^{1}H-NMR and HPLC unless stated otherwise.

Reactions requiring anhydrous conditions were performed under nitrogen in flame-dried apparatus. All temperatures quoted are external.

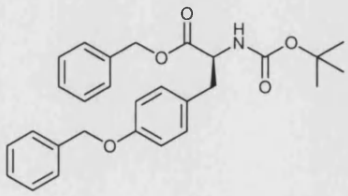
7.2 Compounds from Chapter 2

(*S*)-2-tert-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid, 105



Triethylamine (11.54 mL, 82.8 mmol), Boc anhydride (13.27 g, 60.8 mmol) and tetrabutylammonium iodide (2.55 g, 6.9 mmol) were added to a solution of L-tyrosine (10 g, 55.2 mmol) in dioxane:H_2O (1:1, 100 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 12 hours. The solvent was removed *in vacuo,* and the residue partitioned between water and ethyl acetate. The aqueous layer was washed with ethyl acetate, acidified to pH 1.0 with 2N HCl, and then back-extracted with the same ethyl acetate. The combined organic fractions were washed with brine, dried over magnesium sulphate, filtered and concentrated *in vacuo* yielding **105** as an off-white foam (13.24 g, 47.0 mmol, 85%). $[\alpha]_D^{21}$ + 3.9° (*c* 2.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.42 (9H, s, C*H*$_3$), 3.02 (2H, m, C*H*$_2$Ar), 4.55 (1H, m, C*H*N), 5.14 (1H, br. s, N*H*), 5.97 (1H, br. s, O*H*), 6.70 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.99 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.6 (CH_3), 37.8 (CH_2), 57.8 (CH), 80.5 (C), 116.1 (CH), 129.1 (CH), 131.2 (C), 157.1 (C=O), 157.7 (C), 175.5 (C=O). Spectroscopic data identical to literature compound.[46]

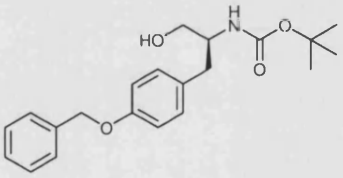
(*S*)-3-(4-Benzyloxy-phenyl)-2-tert-butoxycarbonyl amino-propionic acid benzyl ester, 106



Potassium carbonate (29.59 g, 214.48 mmol), benzyl bromide (20.4 mL, 171.58 mmol) and tetrabutylammonium iodide (1.98 g, 5.36 mmol) were added to a solution of *N*-Boc

protected L-tyrosine **105** (12.1 g, 42.91 mmol) in anhydrous DMF (150 mL). The mixture was stirred for 48 hour at room temperature followed by addition of water and extraction (three times) with ethyl acetate. The organic fractions were combined, washed with 1N HCl and brine, dried over sodium sulphate, and the solvent removed *in vacuo* to afford a dark orange oil that was recrystallised (Et_2O/petrol) to afford the crystalline solid **106** (17.23 g, 37.33 mmol, 87%). m.p. 85-86 °C; $[\alpha]_D^{21}$ -7.9 (*c* 2.97, EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (9H, s, C*H*$_3$), 2.98 (2H, d, *J* 5.6 Hz, C*H*$_2$Ar), 4.52 (1H, m, C*H*N), 4.95 (2H, s, ArOC*H*$_2$Ar), 5.02 (1H, d (as part of ABquartet) *J* 12.0 Hz, (CO)OC*H*AH$_B$Ar), 5.11 (1H, d, (as part of AB quartet, *J* 12.0 Hz, (CO)OC*H*AH$_B$Ar), 6.76 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.87 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.21 - 7.38 (10H, br. m, Ar*H*); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 28.3 (CH_3), 37.4 (CH_2), 54.5 (CH), 67.0 (CH_2), 70.0 (CH_2), 79.9 (C), 114.9 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 129.5 (CH), 129.8 (CH), 130.5 (CH), 131.2 (C), 132.3 (CH), 135.2 (C), 137.0 (C), 155.1 (C=O), 157.8 (C), 171.8 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3423 (N-H), 1729 (C=O), 1701 (C=O); MS (CI+) *m/z* (%) 462 (41) [M+H$^+$], 479 (100) [M+NH_4^+]. Spectroscopic data identical to literature reference.[109]

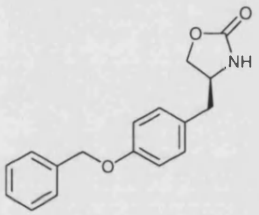
(*S*)-[1-(4-Benzyloxy-benzyl)-2-hydroxyethyl]-carbamic acid *tert*-butyl ester, 107



A solution of ester **106** in THF (40 mL) (9.72 g, 21.06 mmol) was added to a vigorously stirred solution of $LiAlH_4$ (31.59 mL, 1.0 M, 31.59 mmol) in THF at 0 °C over a period of 45 minutes, (CAUTION evolution of hydrogen). The reaction mixture was then stirred at room temperature for one hour before quenching *via* dropwise addition of aqueous potassium hydroxide solution (85 mL, 10%). The resulting solution was then filtered through a pad of Celite® to remove the gelatinous white precipitate, before being extracted with ethyl acetate. The organic layers were combined, washed with brine, dried with magnesium sulphate, and the solvent removed *in vacuo* to afford **107** (6.62 g, 18.53 mmol, 88%) as a cream-coloured powder. m.p. 102-103 °C; Lit. 108-109 °C [110]; $[\alpha]_D^{21}$ -18.0 (*c* 1.74, EtOAc); Lit. -17.0 [110]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (9H, s, C*H*$_3$), 2.68 (2H,

d, *J* 6.8 Hz, CH_2Ar), 3.43 (1H, dd, *J* 10.9, 5.3 Hz, CH_AH$_B$OH), 3.55 (1H, dd, *J* 10.9, 3.8 Hz, CH$_A$$H_B$OH), 3.72 (1H, m, C*H*N), 4.72 (1H, br. s, N*H*), 4.95 (2H, s, OCH_2Ar), 6.83 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.04 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.18-7.37 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.3 (CH_3), 37.5 (CH_2), 54.6 (CH), 67.1 (C), 71.1 (CH_2), 79.9 (CH_2), 114.9 (CH), 130.5 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 135.2 (C), 137.0 (C), 157.9 (C=O), 160.0 (C); IR (KBr) ν_{max} (cm^{-1}): 3367 (broad O-H), 3257 (broad N-H), 1688 (C=O); MS (CI+) m/z (%) 358 (27) [M^+], 319 (93) [M-^{t}Bu+NH_4^+], 301 (100) [M-^{t}Bu$^+$], 240 (39) [M-NHBoc$^+$]; HRMS (ES+) for $C_{21}H_{27}NO_4$ [M+H]$^+$ Calc. 358.2013, Found 358.2015.

(4*S*)-4-(4-Benzyloxy-benzyl)-oxazolidin-2-one, 103



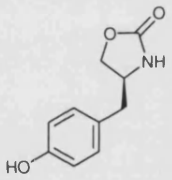
A solution of alcohol **107** in THF (5.2 g, 14.54 mmol) was added to a suspension of sodium hydride (1.45 g, 36.35 mmol) in THF (200 mL) over a period of 20 minutes, stirred for 12 hours, then quenched with saturated ammonium chloride (70 mL). The reaction mixture was then extracted with ethyl acetate (3 x 25 mL)), the organic phase combined, washed with aqueous hydrochloric acid (100 mL, 5% solution), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL), and then dried over magnesium sulphate. Solvent was then removed *in vacuo* to yield **103** (3.12 g, 78%) as a white crystalline solid. m.p. 133-134 °C; Lit. 136-138 °C [43]; $[\alpha]_D^{21}$ -85.1 (*c* 5.05, EtOAc) Lit. - 84.8 [43]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.82 (2H, m, C$H_A$$H_B$Ar), 4.05 (1H, m, C*H*N), 4.15 (1H, dd, *J* 8.5, 5.5 Hz, CH_AH$_B$O), 4.39 (1H, app. t, *J* 8.3 Hz, CH$_A$$H_B$O), 4.98 (2H, s, ArOC$H_2$Ar), 5.05 (1H, br. s, N*H*), 6.87 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.02 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.25 – 7.38 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.2 (CH_2), 54.6 (CH), 70.3 (CH_2), 70.8 (CH_2), 116.7 (CH), 128.3 (CH), 128.8 (CH), 129.0 (CH), 129.4 (CH), 130.9 (C), 137.7 (C), 158.7 (C=O), 160.6 (C); IR (KBr) ν_{max} (cm^{-1}): 3245 (broad N-H), 1753 (C=O); MS (CI+) *m/z* (%) 301 (100)

[M+NH_4^+]. CHN Found C, 71.90, H, 6.05, N, 4.79. $C_{17}H_{17}NO_3$ requires C, 72.07, H, 6.05, N, 4.94. For X-ray crystallography structure, see Appendix.

General Procedure 1: Catalytic hydrogenation

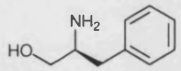
Oxazolidin-2-one (1 equiv.) and Pd/C (0.1 equiv.) were placed in a round-bottomed flask and purged with nitrogen. A mixture of methanol/ ethyl acetate (1:1) was added *via* syringe and the flask placed under 1 atm of hydrogen. The reaction was stirred at room temperature for 18 hours (unless stated otherwise), then filtered through celite and washed thoroughly with ethyl acetate. The solvent was removed *in vacuo* to yield the product.

(*S*)-4-(4-Hydroxy-benzyl)-oxazolidin-2-one, 1



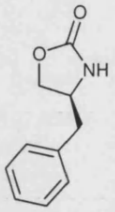
According to General procedure 1 using oxazolidin-2-one **103** (2.00 g, 7.1 mmol), Pd/C (5%) (744 mg, 0.35 mmol) and methanol/ ethyl acetate (1:1, 20 mL), **1** was prepared (1.25 g, 6.49 mmol, 92%) as a white powder. m.p. 179-181 °C; Lit. 175-178 °C [43]; $[\alpha]_D^{21}$ -12.3 (*c* 0.65, MeOH), Lit. -11.8 [35]; ^{1}H NMR (d_4-MeOD, 300 MHz): δ 2.67 (2H, m, CH_AH_BAr), 4.01 (2H, m, CH_AH_BO, C*H*N), 4.27 (1H, m, CH_AH_BO), 6.64 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.95 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOH, 75.5 MHz): δ 41.4 (CH_2), 55.6 (CH), 70.8 (CH_2), 116.8 (CH), 128.6 (CH), 130.9 (C), 157.9 (C), 162.7 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3331 (broad O-H), 3140 (broad N-H), 1731 (C=O); MS (CI+) *m/z* (%) 211 (100) [M+NH_4^+]; HRMS (ES+) for $C_{10}H_{11}NO_3$ [M+NH_4]$^+$ Calc. 211.1077, Found 211.1079.

(*S*)-phenylalanol, 108



L-phenylalanine (5.00g, 30.3 mmol) was placed in a dry 3-necked flask fitted with a reflux condenser and 30 mL dry THF added with the resulting suspension stirred at room temperature. $BF_3.Et_2O$ (3.80 mL, 30.3 mmol) was added dropwise over 15 minutes, and the suspension stirred for a further 15 minutes, before heating at reflux for two hours until the reaction became a colourless and heterogenous solution. $BH_3.SMe_2$ (3.6 mL, 37.8 mmol) was then added over 90 minutes and the solution refluxed for a further 16 hours, before cooling to room temperature. To quench the reaction, THF/ MeOH (1:1, 5mL) and 5M NaOH aq. solution (25 mL) were added dropwise, and the resulting biphasic mixture heated at reflux for six hours. The resulting white precipitate was removed by filtration and the bulk of the solvent removed *in vacuo*. The remaining slurry was extracted into DCM (x3), the combined organic extracts washed with brine and dried over magnesium sulphate. Removal of the solvent yielded a pale yellow solid, which upon recrystallisation furnished **108** (3.26 g, 21.5 mmol, 71%) as a cream-coloured crystalline solid. m.p. 84-85 °C; $[\alpha]_D^{21}$ -21.5 (*c* 1.73 , $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.77 (3H, br. s, O*H*, NH_2), 2.55 (1H, dd, *J* 13.6, 8.7 Hz, CH_AH$_B$Ar), 2.81 (1H, dd, *J* 13.6, 5.3 Hz, CH$_A$$H_B$Ph), 3.13 (1H, m, C*H*N), 3.39 (1H, dd, *J* 10.5, 7.2 Hz, CH_AH$_B$OH), 3.65 (1H, dd, *J* 10.5, 3.7 Hz, CH$_A$$H_B$OH), 7.19 – 7.35 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.1 (CH_2), 54.6 (CH), 66.1 (CH_2), 126.8 (CH), 129.0 (CH), 129.6 (CH), 139.1 (C); IR (KBr) ν_{max} (cm^{-1}): 3355 (broad O-H), 3298 (broad N-H); MS (FAB+) 152 (100) $[M+H]^+$; HRMS (ES+) for $C_9H_{13}NO$ $[M+H]^+$ Calc. 152.1070, Found 152.1072.

(*S*)-4-Benzyl-oxazolidin-2-one, 101



(*S*)-phenylalanol **108** (3.50 g, 23.2 mmol), anhydrous potassium carbonate (320 mg, 2.32 mmol) and diethyl carbonate (5.78 mL, 47.7 mmol) were placed into a round bottomed flask fitted with a Vigreux column, distillation head and receiving flask. The mixture was lowered into an oil bath preheated to 135 °C and stirred until dissolution was achieved. The distillation receiver was then cooled in an ice bath and ca. 2 mL ethanol was collected from the reaction over a five hour period. After the light yellow solution was cooled to ambient temperature, it was diluted with 50 mL DCM, washed with water (x2) and brine before drying over magnesium sulphate and removal of solvent *in vacuo*. Recrystallisation of the resulting pale yellow solid (EtOAc, hexane) produced **101** (3.083 g, 17.4 mmol, 75%) as a white solid. m.p. 84-85 °C, Lit 84.5-86.5 °C [44]; $[\alpha]_D^{21}$ 5.1 ° (*c* 0.77, EtOH), Lit $[\alpha]_D^{21}$ 4.9 ° (*c* 1.10, EtOH)[44]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.88 (2H, m, C*H*$_A$*H*$_B$Ar), 4.09 (1H, m, C*H*N), 4.17 (1H, m, C*H*$_A$H$_B$O), 4.50 (1H, app. t, *J* 8.5 Hz, CH$_A$*H*$_B$O), 5.04 (1H, br. s, N*H*), 7.19 (2H, app. d, *J* 7.0 Hz, Ar*H*), 7.28-7.39 (3H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.8 (CH_2), 54.2 (CH), 70.0 (CH_2), 127.6 (CH), 129.4 (CH), 129.5 (CH), 136.3 (C), 160.1 (C=O); MS (FAB+) 178 (100) $[M+H]^+$; HRMS (ES+) for $C_{10}H_{11}NO_2$ $[M+H]^+$ Calc. 178.0863, Found 178.0864. Spectroscopic data identical to literature compound.[44]

General Procedure 2: Solution phase *N*-acylation employing acid chloride as acyl source

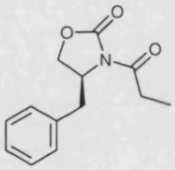
A solution of butyl lithium (1.05 equiv.) was added dropwise to a solution of *N*-H-oxazolidin-2-one (1 equiv.) in THF at –78 °C. The mixture was warmed to 0 °C then cooled back to –78 °C. Acid chloride (1.5 equiv.) was then added and the mixture stirred for 12 hours at room temperature before quenching with H_2O. The aqueous phase was then

extracted into ethyl acetate, washed with H_2O (x 2), and brine (x 2), dried over magnesium sulphate, solvent removed *in vacuo* to afford the *N*-acylated product.

General Procedure 3: Solution phase *N*-acylation employing anhydride as acyl source

Lithium chloride (1.2 equiv.), triethylamine (2 equiv.) and the appropriate anhydride (2 equiv.) were added to a stirred solution of *N*-H-oxazolidin-2-one (1 equiv.) in THF at 0 °C. The mixture was then stirred at reflux for 12 hours, cooled to room temperature and quenched with saturated ammonium chloride solution. The solution was then extracted into ethyl acetate, the organic layer washed with brine, dried over magnesium sulphate and the solvent removed *in vacuo* to afford the *N*-acylated product.

(4*S*)-4-Benzyl-3-propionyl-oxazolidin-2-one, 109

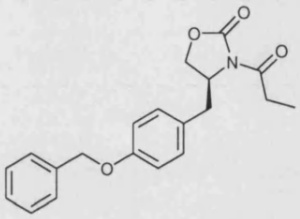


According to General Procedure 2, 4-benzyl-oxazolidin-2-one **101** (401mg, 2.28 mmol) in THF (10 mL) was treated with *n*-BuLi (0.926 mL, 2.58 M, 2.39 mmol) and propionyl chloride (0.298 mL, 3.41 mmol) to afford **109** (490 mg, 2.16 mmol, 92%) as a waxy, white solid. m. p. 41 – 42 °C; $[\alpha]_D^{21}$ + 58.4° (c 0.93, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, t, *J* 7.0 Hz, C*H*$_3$), 2.77 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.95 (2H, m, C*H*$_2$), 3.30 (1H, dd, *J* 13.5 3.5 Hz, CH$_A$*H*$_B$Ar), 4.20 (2H, m, C*H*$_A$*H*$_B$O), 4.67 (1H, m, C*H*N), 7.26 – 7.37 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 300MHz): δ 8.7 (CH_3), 29.6 (CH_2), 37.0 (CH_2), 55.6 (CH), 66.6 (CH_2), 127.7 (CH), 129.3 (CH), 129.8 (CH), 135.7 (C), 153.9 (C=O), 174.5 (C=O). IR (KBr) ν_{max} (cm^{-1}): 1785 (C=O), 1700 (C=O); MS (CI+, NH_3) *m/z* (%) 251 (100) [M+NH_4^+], 234 (12) [M+H^+]; HRMS (ES+) for $C_{13}H_{15}NO_3$ [M+H]$^+$ Calc. 234.1125, Found 234.1121.

109 was also prepared according to General Procedure 3, in which *N*-H-oxazolidin-2-one **101** (250 mg, 1.41 mmol) was treated with lithium chloride (71.6 mg, 1.69 mmol),

triethylamine (0.393 mL, 2.82 mmol) and propionic anhydride (0.361 mL, 2.82 mmol) to afford **109** (293 mg, 1.25 mmol, 89%). Spectroscopic data identical to that reported above.

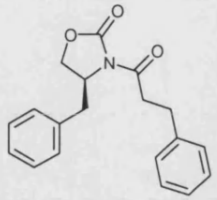
(4*S*)-4-(4-Benzyloxy-benzyl)-3-propionyl-oxazolidin-2-one, 110



According to general procedure 3, *N*-H-oxazolidin-2-one **103** (1.00 g, 3.53 mmol) was treated with lithium chloride (180 mg, 4.24 mmol), triethylamine (0.98 mL, 7.06 mmol) and propionic anhydride (0.91 mL, 7.06 mmol) to afford **110** as a cream solid (995 mg, 2.93 mmol, 83%). m.p. 94-95 °C; $[\alpha]_D^{21}$ + 57 ° (*c* 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, t, *J* 7.3 Hz, C*H*$_3$), 2.73 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.96 (2H, m, C*H*$_2$CH$_3$), 3.22 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 4.20 (2H, m, C*H*$_A$*H*$_B$O), 4.63 (1H, m, C*H*N), 5.02 (2H, s, OC*H*$_2$Ar), 6.94 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.12 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.32 – 7.45 (5H, br. m, Ar*H*); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 8.3 (CH_3), 29.2 (CH_2), 37.0 (CH_2), 55.2 (CH), 66.2 (CH_2), 70.0 (CH_2), 115.3 (CH), 127.4 (CH), 127.5 (C), 128.0 (CH), 128.6 (CH), 130.5 (CH), 136.8 (C), 153.6 (C=O), 158.1 (C), 174.1 (C=O); IR (KBr) ν_{max} (cm^{-1}): 1760 (C=O), 1699 (C=O); MS (CI+) *m/z* (%) 357 (100) [M+NH_4^+]. CHN: Found C, 70.8; H, 6.21; N, 4.11. $C_{20}H_{21}NO_4$ requires C, 70.78; H, 6.24; N, 4.13.

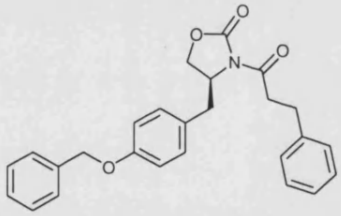
110 also prepared according to general procedure 2, in which *N*-H-oxazolidin-2-one **103** (500 mg, 1.76 mmol) treated with *n*-BuLi (0.74 mL, 2.5 M, 1.85 mmol) and propionyl chloride (0.153 mL, 2.64 mmol) to afford **110** (532 mg, 1.56 mmol, 89%). Spectroscopic data identical to that described above.

(S)-4-benzyl-3-(3-phenylpropanoyl)-oxazolidin-2-one, 111



According to general procedure 2, *N*-H-oxazolidin-2-one **101** (400.0 mg, 2.257 mmol) in THF (15 mL) was treated with *n*-BuLi (0.993 mL, 2.5 M, 2.483 mmol) and 3-phenylpropionyl chloride (0.435 mL, 2.934 mmol) to afford **(*S*)-4-benzyl-3-(3-phenylpropionyl)-oxazolidin-2-one 111** (607 mg, 1.96 mmol, 87%) as a white solid. mp 106-107 °C; $[\alpha]_D^{21}$ + 70 ° (c 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.71 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.05 (2H, m, C*H*$_A$*H*$_B$Ph), 3.20 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.27 (2H, m, COC*H*$_A$*H*$_B$), 4.20 (2H, m, C*H*$_2$O), 4.68 (1H, m, C*H*N), 7.18-7.39 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 30.6 (CH_2), 37.3 (CH_2), 37.5 (CH_2), 55.6 (CH), 66.6 (CH_2), 126.9 (CH), 127.8 (CH), 128.4 (CH), 128.6 (CH), 129.0 (CH), 130.2 (CH), 138.8 (C), 140.2 (C), 154.6 (C=O), 173.1 (C=O). Spectroscopic data identical to literature data. [111]

(*S*)-4-(4-(benzyloxy)benzyl)3-(3-phenylpropionyl)-oxazolidin-2-one, 112



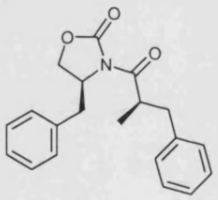
According to General procedure 2, *N*-H-oxazolidin-2-one **103** (500 mg, 1.765 mmol) in THF (20 mL) was treated with *n*-BuLi (0.777 mL, 2.5 M, 1.942 mmol) and 3-phenylpropionyl chloride (0.341 mL, 2.295 mmol) to afford **(*S*)-4-(4-(benzyloxy)benzyl)3-(3-phenylpropionyl)-oxazolidin-2-one 112** (638.2 mg, 1.536 mmol, 87%) as a colourless oil. $[\alpha]_D^{21}$ + 66 ° (c 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.71 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.02 (2H, m, C*H*$_A$*H*$_B$Ph), 3.17 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.27 (2H, m, COC*H*$_A$*H*$_B$), 4.16 (2H, m, C*H*$_2$O), 4.61 (1H, m, C*H*N), 5.04 (2H, s, OC*H*$_2$Ar), 6.92

(2H, app. d, *J* 8.5 Hz, *o*-Ar*H*), 7.08 (2H, app. d, *J* 8.5 Hz, *m*-Ar*H*), 7.18 – 7.45 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 30.6 (CH_2), 37.3 (CH_2), 37.5 (CH_2), 55.6 (CH), 66.6 (CH_2), 70.4 (CH_2), 115.7 (CH), 126.7 (CH), 127.7 (C), 127.9 (CH), 128.4 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 130.9 (CH), 137.2 (C), 140.9 (C), 153.9 (C=O), 158.5 (C), 172.8 (C=O); IR (KBr) ν_{max} (cm^{-1}): 1766 (C=O), 1693 (C=O).

General Procedure 4: Solution phase enolate alkylation reactions

LHMDS (1.0M in THF, 1.5 equiv.) was added dropwise *via* syringe to a solution of *N*-acyl-oxazolidin-2-one (1 equiv.) in anhydrous THF at –78 °C. After 30 minutes, the electrophile (3 equiv.) was added in one portion and the resulting solution stirred for two hours at -78 °C, followed by 12 hours at -15 °C. The reaction was quenched by addition of saturated ammonium chloride solution and extracted into ethyl acetate (x3). The combined organic fractions were washed with brine (x1), dried over $MgSO_4$ and solvent removed *in vacuo* to yield the product.

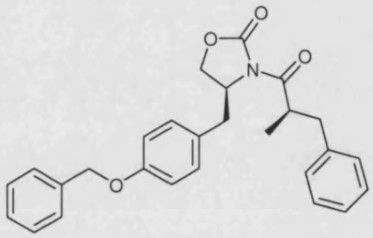
(4*S*)-4-Benzyl-3-((2*R*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 114



According to General procedure 4 using *N*-acyl oxazolidinone **109** (100 mg, 0.43 mmol), LHMDS (0.64 mL, 0.64 mmol) and benzyl bromide (0.25 mL, 2.14 mmol), a crude mixture containing the product was prepared as a pale yellow solid. Recrystallisation (ethyl acetate/ petroleum ether b.p. 40-60°C) afforded **114** as needles of white crystals (121 mg, 0.37 mmol, 87%). m. p. 88–89 °C; $[\alpha]_D^{21}$ + 12 ° (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, d, *J* 7.0 Hz, C*H*$_3$), 2.55 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.64 (1H, dd, *J* 13.0, 7.5 Hz, CH(CH$_3$)C*H*$_A$H$_B$), 3.05 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.15 (1H, dd, *J* 13.0, 7.0 Hz, CH(CH$_3$)CH$_A$*H*$_B$), 4.04 – 4.19 (3H, br. m, C*H*$_A$*H*$_B$O, C*H*CH$_3$), 4.65 (1H, m, C*H*N), 7.03 (2H, app. d, *J* 7.5 Hz, Ar*H*), 7.18 – 7.30 (8H, br. m, Ar*H*); ^{13}C NMR

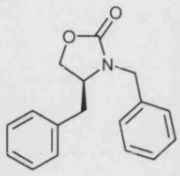
($CDCl_3$, 75.5 MHz): δ 16.7 (CH_3), 37.6 (CH_2), 39.6 (CH), 39.8 (CH_2), 55.1 (CH)), 65.9 (CH_2), 126.4 (CH), 127.3 (CH), 128.3 (CH), 128.9 (CH), 129.3 (CH), 129.4 (CH), 135.1 (C), 139.2 (C), 153.0 (C=O), 176.5 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3022 (C_{Ar}-H), 2912 (C-H), 1764 (C=O), 1700 (C=O), 1559 (C_{Ar}-C_{Ar}), 1454 (C-H), 1388 (C-H), 1240 (C-O), 746 (C_{Ar}-H), 700 (C_{Ar}-H); MS (CI+, NH_3) *m/z* (%) 341 (100) [M+NH_4^+], 324 (38) [M+H^+].

(4*S*)-4-(4-Benzyloxy-benzyl)-3-((2*R*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 115



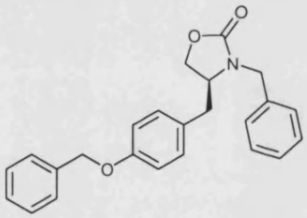
According to General procedure 4 using *N*-propionyl-oxazolidinone **110** (100 mg, 0.29 mmol), LHMDS (0.44 mL, 1.0 M, 0.44 mmol) and benzyl bromide (0.105 mL, 0.89 mmol), a crude mixture of the product was prepared as an off-white solid. Column chromatography on silica using 10:1 petroleum ether (b.p.40-60°C)/ethyl acetate as the eluent yielded **115** as needles of a white crystalline solid (111 mg, 0.26 mmol, 89%). m. p. 123-124 °C; $[\alpha]_D^{21}$ +13 ° (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.11 (3H, d, *J* 7.0 Hz, CH_3), 2.44 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH_BAr), 2.59 (1H, dd,, *J* 13.0, 7.5 Hz, $CH(CH_3)CH_AH_B$), 2.89 (1H, dd, *J* 13.5, 3.5 Hz, CH_AH_BAr), 3.0 (1H, dd, *J* 13.0, 7.0 Hz, $CH(CH_3)CH_AH_B$), 3.98 – 4.11 (3H, br. m, CH_AH_BO, $CHCH_3$), 4.53 (1H, m, CHN), 4.94 (2H, s, $ArOCH_2Ar$), 6.78 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.85 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.09 – 7.36 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.4 (CH_3), 37.0 (CH_2), 39.9 (CH), 40.1 (CH_2), 55.4 (CH), 66.1 (CH_2), 70.2 (CH_2), 115.5 (CH), 126.7 (CH), 127.6 (C), 127.7 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 129.7 (CH), 130.7 (CH), 137.2 (C), 139.6 (C), 153.4 (C=O), 158.3 (C), 176.7 (C=O); IR (KBr) ν_{max} (cm^{-1}): 1768 (C=O), 1688 (C=O); MS (CI+, NH_3) *m/z* (%) 447 (9) [M+NH_4^+], 98 (100); HRMS (ES+) for $C_{27}H_{27}NO_4$ [M+NH_4]$^+$ Calc. 447.2278, Found 447.2277.

(4*S*)-3,4-dibenzyl-oxazolidin-2-one, 121



Purification *via* column chromatography of the crude reaction product of the attempted alkylation of **109** with benzyl bromide at -78°C to room temperature afforded **(4*S*)-3,4-dibenzyl-oxazolidin-2-one 121** (14.9 mg, 0.056 mmol, 13%) as a colourless oil. $[\alpha]_D^{21}$ -11.4 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.60 (1H, dd, *J* 13.5, 9.5 Hz, CCH_AH_BPh), 3.04 (1H, dd, *J* 13.5, 3.5 Hz, CCH_AH_BPh), 3.79 (1H, m, C*H*N), 4.01 (1H, dd, *J* 8.5, 5.5 Hz, CH_AH_BO), 4.11 (2H, m, CH_AH_BO, NCH_AH_BPh), 4.88 (1H, d *J* 15.0 Hz, NCH_AH_BPh), 7.02-7.10 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 38.5 (CH_2), 46.6 (CH_2), 55.8 (CH), 68.1 (CH_2), 127.3 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 129.3 (CH), 135.8 (C), 137.2 (C), 158.6 (C=O). Spectroscopic data identical to literature compound [112]

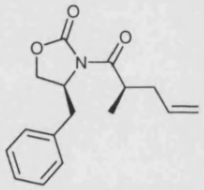
(4*S*)-3-Benzyl-4-(4-benzyloxy-benzyl)-oxazolidin-2-one, 122



Purification *via* column chromatography of the crude reaction product of the attempted alkylation of **110** with benzyl bromide at -78°C to room temperature afforded **(4*S*)-3-Benzyl-4-(4-benzyloxy-benzyl)-oxazolidin-2-one 122** (15.2 mg, 0.04 mmol, 14%) as a pale yellow oil. $[\alpha]_D^{21}$ + 90.9° (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH_BAr), 3.03 (1H, dd, *J* 13.5, 3.5 Hz, CH_AH_BAr), 3.75 (1H, m, C*H*N), 3.99 (1H, dd, *J* 8.5, 6.0 Hz, CH_AH_BO), 4.10 (2H, m, CH_AH_BO, NCH_AH_B), 4.86 (1H, d, *J* 15.0 Hz, NCH_AH_B), 5.04 (2H, s, OCH_2Ar), 6.92 (2H, app. d, *J* 8.5 Hz, *o*-OArH), 6.95 (2H, app. d, *J* 8.5 Hz, *m*-OArH), 7.23 – 7.44 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$,

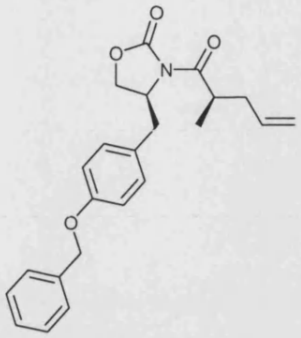
75.5 MHz): δ 37.5 (CH_2), 46.3 (CH_2), 55.3 (CH), 66.9 (CH_2), 70.0 (CH_2), 115.2 (CH), 127.4 (CH), 127.6 (CH), 127.9 (CH), 128.0 (C), 128.2 (CH), 128.6 (CH), 128.9 (CH), 130.0 (CH), 135.9 (C), 136.8 (C), 157.9 (C=O), 158.4 (C); IR (thin film) ν_{max} (cm^{-1}): 1742 (C=O); MS (EI+) *m/z* (%) 374 (38) [M^{+}]; HRMS (ES+) for $C_{24}H_{23}NO_3$ [M+H]$^+$ Calc. 374.1751, Found 374.1752.

(*S*)-3-((*R*)-2-methylpent-4-enoyl)-4-benzyl-oxazolidin-2-one, 125



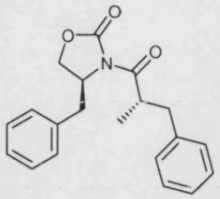
According to General procedure 4 using *N*-propionyl-oxazolidinone **109** (100.0 mg, 0.428 mmol), LHMDS (0.64 mL, 1.0M, 0.64 mmol) and allyl iodide (0.195 mL, 2.14 mmol), a crude mixture containing the product was prepared as a pale yellow solid. Recrystallisation (ethyl acetate/ hexane) afforded **(*S*)-3-((*R*)-2-methylpent-4-enoyl)-4-benzyl-oxazolidin-2-one 125** as needles of colourless crystals (102.9 mg, 0.376 mmol, 88%). $[\alpha]_D^{21}$ 92 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (3H, d, *J* 7.0 Hz, CH_3), 2.20 (1H, m, $CH(CH_3)CH_AH_B$), 2.49 (1H, m, $CH(CH_3)CH_AH_B$), 2.60 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH_BAr), 3.18 (1H, dd, *J* 13.5, 3.5 Hz, CH_AH_BAr), 3.84 (1H, m, $CHCH_3$), 4.12 (2H, m, CH_AH_BO), 4.59 (1H, m, CHN), 5.05 (2H, m, $C=CH_2$), 5.78 (1H, m, $HC=CH_2$), 7.26 – 7.38 (5H, br. m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.6 (CH_3), 37.3 (CH), 37.8 (CH_2), 38.2 (CH_2), 55.7 (CH), 66.0 (CH_2), 117.5 (CH_2), 127.8 (CH), 128.6 (C), 129.3 (CH), 134.8 (CH), 135.7 (CH), 153.0 (C=O), 176.4 (C=O). Spectroscopic data identical to literature data.[113]

4*S*-(4-Benzyloxybenzyl)-3-((2*R*)-2-methyl-pent-4-enoyl)-oxazolidin-2-one, 126



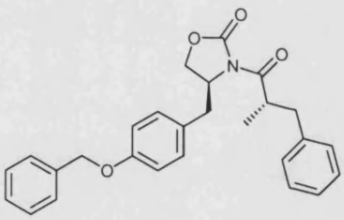
According to General procedure **4** using *N*-acyl-oxazolidinone **110** (80 mg, 0.24 mmol), LHMDS (0.35 mL, 1.0 M, 0.35 mmol) and allyl iodide (0.065 mL, 0.71 mmol), the crude product was prepared as a dark yellow oil. Column chromatography on silica using 4:1 petroleum ether (b.p.40-60°C)/ethyl acetate as the eluent yielded **126** as a colourless oil (81.0 mg, 0.214 mmol, 89%). $[\alpha]_D^{21}$ + 36.5° (c 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.11 (3H, d, *J* 7.2 Hz, C*H*$_3$), 2.16 (1H, m, CH(CH$_3$)C*H*$_A$H$_B$), 2.45 (1H, m, CH(CH$_3$)CH$_A$*H*$_B$), 2.57 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.13 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.78 (1H, m, C*H*CH$_3$), 4.08 (2H, m, C*H*$_A$*H*$_B$O), 4.56 (1H, m, C*H*N), 4.97 (2H, s, OC*H*$_2$Ar), 5.03 (2H, m, C=C*H*$_2$), 5.75 (1H, m, *H*C=CH$_2$), 6.86 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.06 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.23 – 7.37 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.8 (CH_3), 37.5 (CH), 37.6 (CH_2), 38.4 (CH_2), 55.9 (CH), 66.4 (CH_2), 70.5 (CH_2), 115.7 (CH), 117.8 (CH_2), 127.9 (CH), 128.0 (C), 128.4 (CH), 129.0 (C), 130.9 (CH), 135.7 (CH), 137.3 (C), 153.6 (C=O), 158.5 (C), 176.9 (C=O); IR (Thin film) ν_{max} (cm^{-1}): 1770 (C=O), 1694 (C=O); MS (CI+, NH_3) m/z (%) 397 (100) [M+NH_4^+], 380 (38) [M+H^+]; HRMS (ES+) for $C_{23}H_{25}NO_4$ [M+NH_4]$^+$ Calc. 397.2122 , Found 397.2122.

(4*S*)-4-Benzyl-3-((2*S*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 123



According to general procedure 4, using *N*-3-phenyl-propionyl-oxazolidin-2-one **111** (100 mg, 0.323 mmol), LHMDS (0.484 mL, 1.0M in THF, 0.484 mmol) and methyl iodide (0.060 mL, 0.969 mmol) to afford crude **123** as a yellow oil. Purification *via* column chromatography afforded **123** as a colourless oil (86.7 mg, 0.268 mmol, 83%). $[\alpha]_D^{21}$ 63 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (3H, d, *J* 7.0 Hz, CH_3), 2.60 – 2.71 (2H, m, CH_AH_BAr and $CH(CH_3)CH_AH_B$), 3.05 (1H, dd, *J* 13.0, 7.5 Hz, $CH(CH_3)CH_AH_B$), 3.14 (1H, dd, *J* 13.5, 3.5 Hz, CH_AH_BAr), 3.89 (1H, app. t, *J* 8.5 Hz, CH_AH_BO), 4.08 (1H, dd, *J* 9.0, 2.0 Hz, CH_AH_BO), 4.13 (1H, q, *J* 7.0 Hz, $CHCH_3$), 4.42 (1H, m, CHN), 6.99-7.32 (10H, br. m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 17.4 (CH_3), 37.0 (CH_2), 39.6 (CH), 39.9 (CH_2), 55.4 (CH), 66.2 (CH_2), 126.5 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 129.4 (CH), 129.9 (CH), 137.2 (C), 137.8 (C), 153.6 (C=O), 175.9 (C=O); IR and mass spec data identical to 4*S*,2*R*-**114**.

(4*S*)-4-(4-Benzyloxy-benzyl)-3-((2*S*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 124



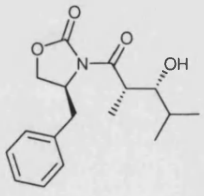
According to General procedure 4, using *N*-3-phenyl-propionyl-oxazolidin-2-one **112** (100 mg, 0.24 mmol), LHMDS (0.36 mL, 1.0M in THF, 0.36 mmol) and methyl iodide (0.044 mL, 0.72 mmol) to afford crude **124** as a yellow oil. Purification *via* column chromatography afforded **124** as a colourless oil (84.5 mg, 0.197 mmol, 82%). $[\alpha]_D^{21}$ + 70 ° (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, d, *J* 7.0 Hz, CH_3), 2.64 – 2.74 (2H, m, CH_AH_BAr and $CH(CH_3)CH_AH_B$), 3.03 (1H, dd, *J* 13.0, 7.5 Hz, $CH(CH_3)CH_AH_B$),

3.15 (1H, dd, *J* 13.5, 3.5 Hz, CH_AH_BAr), 3.94 (1H, app. t, *J* 8.5 Hz, CH_AH_BO), 4.06 (1H, dd, *J* 9.0, 2.2 Hz, CH_AH_BO), 4.11 (1H, q, *J* 7.0 Hz, $CHCH_3$), 4.46 (1H, m, CHN), 5.03 (2H, s, $ArOCH_2Ar$), 6.92 (2H, app. d, *J* 8.5 Hz, *o*-OArH), 7.10 (2H, app. d, *J* 8.5 Hz, *m*-OArH), 7.15 – 7.44 (10H, br. m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 17.5 (CH_3), 37.4 (CH_2), 39.9 (CH), 40.3 (CH_2), 55.8 (CH), 66.4 (CH_2), 70.4 (CH_2), 115.6 (CH), 126.8 (CH), 127.8 (C), 127.9 (CH), 128.4 (CH), 128.7 (CH), 129.0 (CH), 129.6 (CH), 130.9 (CH), 137.2 (C), 139.6 (C), 153.4 (C=O), 158.5 (C), 176.9 (C=O). IR and mass spec data identical to 4*S*,2*R*-**115**.

General Procedure 5: Solution phase *syn*-aldol reactions

9-BBN-OTf (0.5 M in DCM, 1.1 equiv.) was added dropwise *via* syringe to a stirred solution of *N*-acyl oxazolidinone (1 equiv.) in DCM at 0 °C. After 30 minutes, DIPEA (1.2 equiv.) was added and the solution stirred for a further 30 minutes before cooling to -78 °C and the addition of aldehyde (1.2 equiv.). The resulting solution was stirred at -78 °C and allowed to slowly warm to room temperature over the stated period of time. In order to quench the reaction, phosphate buffer pH 7 (0.1 M) was added, followed by a solution of H_2O_2 in MeOH (2:1 v/v) and the mixture was stirred for 6 hours. Finally the reaction was extracted into DCM (x3), the combined organic fractions were washed with saturated sodium bicarbonate solution (x2) and brine (x1), dried over magnesium sulphate and solvent removed *in vacuo* to afford the crude product.

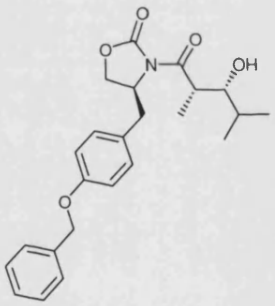
(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethyl-pentanoyl)-oxazolidin-2-one, 133



According to general procedure 5 employing *N*-propionyl-oxazolidin-2-one **109** (200 mg, 0.857 mmol) in DCM (8 mL), 9-BBN-OTf (1.885 mL, 0.5 M, 0.943 mmol), $^iPr_2NEt$ (0.179 mL, 1.028 mmol) and isobutyraldehyde (0.094 mL, 1.028 mmol), the crude product was

prepared as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,4-dimethyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 133** (186 mg, 0.608 mmol, 71%) as a colourless oil. $[\alpha]_D^{21}$ + 41 ° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.98 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.02 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.21 (3H, d, *J* 7.2 Hz, C*H*$_3$), 1.70 (1H, m, C*H*$(CH_3)_2$), 2.78 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.98 (1H, br. s, O*H*), 3.23 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.54 (1H, m, C*H*OH), 3.98 (1H, dq, *J* 3.0, 7.0 Hz, C*H*CH$_3$), 4.21 (2H, m, C*H*$_A$*H*$_B$O), 4.69 (1H, m, C*H*N), 7.28-7.39 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.8 (CH_3), 18.7 (CH_3), 19.2 (CH_3), 30.6 (CH), 37.6 (CH), 39.5 (CH_2), 55.2 (CH), 66.0 (CH_2), 77.8 (CH), 127.3 (CH), 128.9 (CH), 129.5 (CH), 135.0 (C), 152.8 (C=O), 177.7 (C=O); Spectroscopic data essentially identical to literature compound [114]

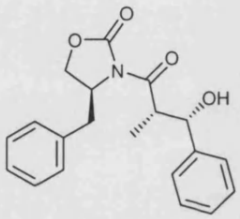
(*S*)-4-(4-Benzyloxy-benzyl)-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethyl-pentanoyl)-oxazolidin-2-one, 134



According to general procedure 5, employing *N*-propionyl-oxazolidin-2-one **110** (200 mg, 0.589 mmol) in DCM (8 mL), 9-BBN-OTf (1.296 mL, 0.5 M, 0.648 mmol), $^iPr_2NEt$ (0.123 mL, 0.707 mmol) and isobutyraldehyde (0.064 mL, 0.707 mmol), the crude product was prepared as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-(4-Benzyloxy-benzyl)-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethyl-pentanoyl)-oxazolidin-2-one 134** (176.9 mg, 0.430 mmol, 73%) as a colourless oil. $[\alpha]_D^{21}$ + 48 ° (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.00 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.04 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.22 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.70 (1H, m, C*H*$(CH_3)_2$), 2.80 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.82 (1H, br. s, O*H*), 3.25 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.56 (1H, m, C*H*OH), 3.99 (1H, dq, *J* 7.0, 3.0 Hz, C*H*CH$_3$), 4.24 (2H, m, C*H*$_A$*H*$_B$O), 4.66 (1H, m, C*H*N),

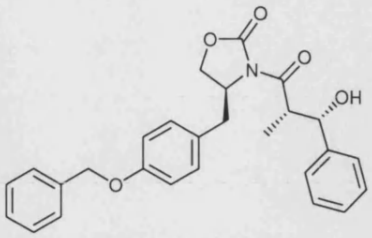
5.01 (2H, s, ArOCH_2Ar), 6.89 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.00 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.15-7.39 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 9.9 (CH_3), 18.5 (CH_3), 19.4 (CH_3), 30.8 (CH), 37.4 (CH), 38.9 (CH_2), 55.4 (CH), 66.4 (CH_2), 70.4 (CH_2), 77.4 (CH), 115.7 (CH), 126.9 (CH), 127.4 (C), 128.3 (CH), 128.4 (CH), 130.9 (C), 137.4 (C), 153.9 (C=O), 158.6 (C), 176.8 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3532 (broad O-H), 1783 (C=O), 1688 (C=O).

(4*S*)-4-Benzyl-3-((3*S*)-3-hydroxy-(2*S*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 135



According to General Procedure 5 using *N*-acyl-oxazolidinone **109** (150 mg, 0.44 mmol), 9-BBN-OTf (1.06 mL, 0.5 M, 0.53 mmol), DIPEA (0.100 mL, 0.58 mmol) and benzaldehyde (0.049 mL, 0.49 mmol), the crude product was prepared as a dark yellow oil. Column chromatography on silica using 10:1 petroleum ether (b.p.40-60 °C)/ethyl acetate yielded **135** as a colourless oil (112 mg, 0.33 mmol, 75%); $[\alpha]_D^{21}$ + 54 ° (*c* 1.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (3H, d, *J* 7.0 Hz, CH_3), 2.68 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH$_B$Ar), 3.10 (1H, br. s, O*H*), 3.15 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$$H_B$Ar), 4.01 (3H, m, C*H*CH$_3$, C$H_A$$H_B$O), 4.49 (1H, m, C*H*N), 5.00 (1H, app. d, *J* 4.0 Hz, C*H*OH), 7.22 (10H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.4 (CH_3), 38.1 (CH_2), 45.0 (CH), 55.6 (CH), 66.6 (CH_2), 74.2 (CH), 126.5 (CH), 127.8 (CH), 127.9 (CH), 128.6 (CH), 129.4 (CH), 129.8 (CH), 135.4 (C), 141.7 (C), 153.3 (C=O), 177.1 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3507 (broad O-H), 1770 (C=O), 1698 (C=O); MS (EI+) *m/z* (%) 339 (2) [M^+], 57 (100); MS (CI+, NH_3) *m/z* (%) 357 (5) [M+NH_4^+], 251 (100); HRMS (ES+) for $C_{20}H_{21}NO_4$ [M+H]$^+$ Calc. 340.1543, Found 340.1543.

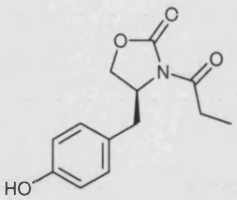
(4*S*)-4-(4-Benzyloxy-benzyl)-3-((3*S*)-3-hydroxy-(2*S*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 136



According to General Procedure 5 using *N*-acyl oxazolidinone **110** (200 mg, 0.59 mmol), 9-BBN-OTf (1.42 mL, 0.5 M, 0.71 mmol), DIPEA (0.133 mL, 0.77 mmol) and benzaldehyde (0.066 mL, 0.65 mmol), the crude product was prepared as a yellow oil. Column chromatography on silica using 10:1 petroleum ether (b.p.40-60 °C)/ethyl acetate as the eluent yielded **136** as needles of a white crystalline solid (157 mg, 0.35 mmol, 69%). m.p. 102-103 °C; $[\alpha]_D^{21}$ + 50 ° (*c* 3.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.12 (3H, d, *J* 7.0 Hz, C*H*$_3$), 2.61 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.04 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.15 (1H, br. s, O*H*), 3.92 (1H, m, C*H*CH$_3$), 4.00 (2H, m, C*H*$_A$*H*$_B$O), 4.41 (1H, m, C*H*N), 4.93 (2H, s, ArOC*H*$_2$Ar), 4.97 (1H, app. d, *J* 4.0 Hz, C*H*OH), 6.83 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.00 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.12-7.35 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.4 (CH_3), 37.2 (CH_2), 45.0 (CH), 55.7 (CH), 66.6 (CH_2), 70.5 (CH_2), 74.3 (CH), 115.7 (CH), 126.6 (CH), 127.6 (C), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 130.9 (CH), 137.3 (C), 141.8 (C), 153.4 (C=O), 158.5 (C), 177.1 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3540 (broad O-H), 1781 (C=O), 1689 (C=O); MS (CI+, NH_3) *m/z* (%) 463 (100) $[M+NH_3]^+$, 446 (84) $[M+H]^+$; HRMS (ES+) for $C_{27}H_{27}NO_5$ $[M+NH_4]^+$ Calc. 463.2227, Found 463.2230. CHN: Found C, 72.6; H, 6.07; N, 2.97. $C_{27}H_{27}NO_5$ requires C, 72.79; H, 6.11; N, 3.14.

7.3 Compounds from Chapter 3

(4*S*)-4-(4-Hydroxy-benzyl)-3-propionyl-oxazolidin-2-one, 144



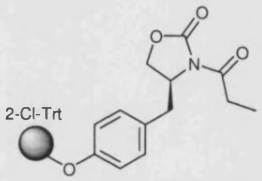
According to General procedure 1, using *N*-acyl oxazolidinone **110** (1.53 g, 4.50 mmol), Pd/C (5%) (237 mg, 0.23 mmol) and methanol/ethyl acetate (1:1, 20 mL), **144** was prepared (1.14 g, 4.59 mmol, 98%) as a white powder. m. p. 135 – 136 °C; $[\alpha]_D^{21}$ + 43° (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (3H, t, *J* 7.0 Hz, C*H*$_3$), 2.66 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.89 (2H, m, C*H*$_2$CH$_3$), 3.13 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 4.12 (2H, m, C*H*$_A$*H*$_B$O), 4.55 (1H, m, C*H*N), 4.78 (1H, br. s, O*H*), 6.73 (2H, app. d, *J* 8.5 Hz, H-*o*-OAr*H*), 7.00 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 9.2 (CH_3), 30.4 (CH_2), 37.8 (CH_2), 56.8 (CH), 68.1 (CH_2), 116.9 (CH), 127.8 (C), 132.0 (CH), 156.0 (C=O), 158.1 (C), 176.1(C=O); IR (KBr) ν_{max} (cm^{-1}): 3331 (broad O-H), 1756 (C=O), 1709 (C=O); MS (CI+, NH_3) *m/z* (%) 267 (52) [M+NH_4^+], 91 (100); HRMS (ES+) for $C_{13}H_{15}NO_4$ [M+NH_4]$^+$ Calc. 267.1339, Found 267.1343.

General Procedure 6: Immobilisation of phenolic oxazolidin-2-one fragments onto 2-chlorotrityl cloride resin.

2-chlorotrityl chloride resin (1 equiv.) was preswollen in DCM:THF (1:1 mixture) at ambient temperature in a vessel fitted with a reflux condenser. A solution of phenolic oxazolidin-2-one fragment (3 equiv.) in DCM / THF (1:1) (plus a minimum of DMF if necessary to ensure solvation) was added, followed by diisopropylethylamine (10 equiv.) and the reaction heated at 60 °C for 18 hours. After this time, the reaction was cooled to ambient temperature and the resin removed *via* filtration. The resin was washed thoroughly with DCM, THF and DCM / MeOH, with all washings collected. In order to recover the excess oxazolidin-2-one fragment, the combined washings were evaporated to dryness, redissolved in methanol and passed through a solid phase extraction column (SCX-2) with

the resulting filtrate evaporated to yield pure oxazolidin-2-one. Meanwhile, the resin was dried thoroughly in a vacuum oven at 40 °C. A portion of the resultant resin (typically 20mg) was cleaved with TFA solution, according to General Procedure 8, and the mass of the recovered oxazolidin-2-one fragment was used to calculate the loading of oxazolidin-2-one onto the 2-chlorotrityl chloride resin.

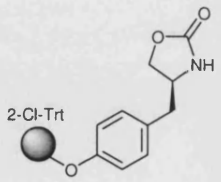
2-Cl-Trt-supported *N*-propionyl-oxazolidin-2-one, 145



According to general procedure 6, 2-chlorotrityl-chloride resin (1.00g, 1.20 mmol) preswollen in DCM / THF (80 mL) was treated with *N*-propionyl-oxazolidin-2-one **144** (897 mg, 3.6 mmol) and DIPEA (2.090 mL, 12.0 mmol) to afford polymer-supported *N*-propionyl-oxazolidin-2-one **145**.

To determine the loading of the resin: Functionalised resin **145** (20 mg) was treated with TFA cleavage solution, according to general procedure 8. In this way the resin loading was found to be 1.11 $mmolg^{-1}$ (93%).

2-Cl-Trt-supported *N*-H-oxazolidin-2-one, 2



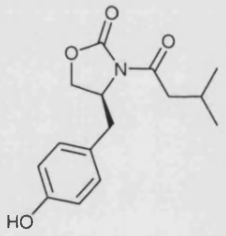
According to general procedure 6, 2-chlorotrityl-chloride resin (1.00g, 1.20 mmol) preswollen in DCM / THF (80 mL) was treated with *N*-H-oxazolidin-2-one **1** (695 mg, 3.6 mmol) and DIPEA (2.090 mL, 12.0 mmol) to afford polymer-supported *N*-H-oxazolidin-2-one **2**.

To determine the loading of the resin: Functionalised resin **2** (20 mg) was treated with TFA cleavage solution, according to general procedure 8. In this way the resin loading was found to be 1.16 $mmolg^{-1}$ (97%).

General procedure 7: *N*-acylation of polymer-supported *N*-H-oxazolidin-2-one employing anhydride as acyl source

N-H-oxazolidin-2-one functionalised resin (1 equiv.) encased in IRORI kans was preswollen in THF at room temperature. Lithium chloride (5 equiv.), triethylamine (5 equiv.) and the anhydride (5 equiv.) were added and the reaction then heated at reflux for 16 hours. After this time, the reaction was cooled to ambient temperature and the resin removed *via* filtration. The resin was then washed thoroughly with DCM, THF, DCM / MeOH and dried in a vacuum oven at 40 °C.

(*S*)-3-(3-methylbutanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 154

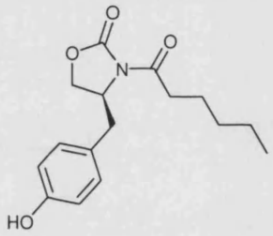


According to General procedure 7 employing *N*-H oxazolidin-2-one functionalised resin **2** (1.00 g, 1.10 mmol/g, 1.10 mmol) in THF (300 mL), LiCl (233 mg, 5.5 mmol), triethylamine (0.767 mL, 5.5 mmol) and isovaleric anhydride (1.10 mL, 5.5 mmol), *N*-isovaleryl-oxazolidin-2-one functionalised resin **151** was prepared (structure not shown).

TFA cleavage: According to General procedure 8 employing *N*-isovaleryl-oxazolidin-2-one functionalised resin **151** (50 mg, 0.055 mmol), TFA cleavage solution (5 mL) **(*S*)-3-(3-methylbutanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one 154** (13.9 mg, 0.050 mmol, 91%) was prepared as a colourless oil. $[\alpha]_D^{21}$ + 36° (1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.02 (6H, app. t, *J* 6.5 Hz, CH_3), 2.23 (1H, m, $CH(CH_3)_2$), 2.71 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH_BAr), 2.78 (1H, dd, *J* 16.0, 7.0 Hz, $COCH_AH_B$), 2.89 (1H, dd, *J* 16.0, 6.5 Hz, $COCH_AH_B$), 3.21 (1H, dd, *J* 13.5, 3.5 Hz, CH_AH_BAr), 4.19 (2H, m, CH_AH_BO), 4.64 (1H,

m, C*H*N), 5.04 (br. s, O*H*), 6.80 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.08 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.8 (CH_3), 22.9 (CH_3), 25.4 (CH), 37.5 (CH_2), 44.4 (CH_2), 55.6 (CH), 66.5 (CH_2), 116.2 (CH), 127.7 (C), 131.0 (CH), 153.9 (C=O), 155.3 (C), 175.1 (C=O); IR (thin film): ν_{max} (cm^{-1}): 3362 (broad OH), 1763 (C=O), 1710 (C=O); MS (CI+, NH_3) *m/z* (%) 295 (70) $[M+NH_3]^+$, 278 (33) $[M+H]^+$, 119 (100); HRMS (ES+) for $C_{15}H_{19}NO_4$ $[M+NH_4]^+$ Calc. 295.1652, Found 295.1654.

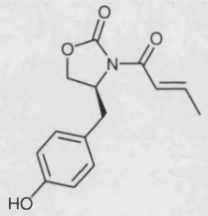
(*S*)-4-(4-hydroxybenzyl)-3-hexanoyl-oxazolidin-2-one, 155



According to General procedure 7 (solid phase *N*-acylation) employing *N*-H oxazolidin-2-one functionalised resin **2** (1.00 g, 0.91 mmol/g, 0.91 mmol) in THF (300 mL), LiCl (193 mg, 4.55 mmol), triethylamine (0.634 mL, 4.55 mmol) and hexanoic anhydride (1.050 mL, 4.55 mmol), *N*-hexanoyl-oxazolidin-2-one functionalised resin **152** was prepared (structure not shown). TFA cleavage: According to General procedure 8 (TFA cleavage) employing *N*-hexanoyl-oxazolidin-2-one functionalised resin **152** (50 mg, 0.046 mmol), TFA cleavage solution (5 mL) **(*S*)-4-(4-hydroxybenzyl)-3-hexanoyloxazolidin-2-one 155** (9.9 mg, 0.034 mmol, 75%) was prepared as an off-white solid. m.p. 117-119 °C ; $[\alpha]_D^{21}$ + 52 ° (*c* 0.78, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (3H, t, *J* 7.0 Hz, C*H*$_3$), 1.35 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 1.69 (2H, m, C*H*$_2$(CH$_2$)$_2$CH$_3$), 2.72 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.92 (2H, m, COC*H*$_2$), 3.17 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 4.15 (1H, dd, *J* 9.0, 3.0 Hz, C*H*$_A$H$_B$O), 4.19 (1H, dd, *J* 16.5, 9.0 Hz, CH$_A$*H*$_B$O), 4.62 (1H, m, C*H*N), 5.58 (1H, br. s, O*H*), 6.79 (2H, app. d, *J* 8.5, *o*-OAr*H*), 7.05 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*) ; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.3 (CH_3), 22.8 (CH_2), 24.4 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 37.4 (CH_2), 55.6 (CH), 66.6 (CH_2), 116.2 (CH), 127.5 (C), 131.0 (CH), 154.0 (C=O), 155.4 (C), 174.0 (C=O) ; IR (KBr) ν_{max} (cm^{-1}): 3308 (O-H), 1751 (C=O), 1708 (C=O); MS (CI+,

NH_3) *m/z* (%) 309 (100) $[M+NH_4]^+$, 292 (23) $[M+H]^+$, 211 (25), 133 (39); HRMS (ES+) for $C_{16}H_{21}NO_4$ $[M+H]^+$ Calc. 292.1543, Found 292.1543.

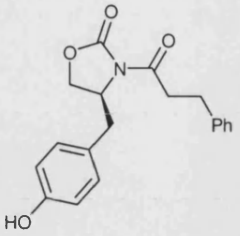
(*S*)-3-((*E*)-but-2-enoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 156



According to General procedure 7 (solid phase acylation) employing *N*-H oxazolidin-2-one functionalised resin **2** (1.00 g, 1.05 mmol/g, 1.05 mmol) in THF (300 mL), LiCl (223 mg, 5.25 mmol), triethylamine (0.732 mL, 5.25 mmol) and crotonic anhydride (0.778 mL, 5.25 mmol), *N*-crotonoyl-oxazolidin-2-one functionalised resin **153** was prepared (structure not shown).

TFA cleavage: According to General procedure 8 (TFA cleavage) employing *N*-crotonoyl-oxazolidin-2-one functionalised resin **153** (50 mg, 0.053 mmol), TFA cleavage solution (5 mL) **(*S*)-3-((*E*)-but-2-enoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one 156** (10.4 mg, 0.040 mmol, 75%) was prepared as a colourless oil. $[\alpha]_D^{21}$ + 64 ° (*c* 1.41, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.94 (3H, d, *J* 6.0 Hz, C*H*$_3$), 2.74 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.21 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 4.15 (2H, m, C*H*$_2$O), 4.65 (1H, m, C*H*N), 6.91 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.07 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.15-7.23 (2H, br. m, *H*C=C*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 18.9 (CH_3), 37.4 (CH_2), 55.8 (CH), 66.5 (CH_2), 115.7 (CH), 122.3 (CH), 127.9 (C), 128.6 (CH), 147.2 (CH), 153.6 (C=O), 157.3 (C), 174,2 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3365 (broad O-H), 1785 (C=O), 1686 (C=O); MS (CI+, NH_3) *m/z* (%) 279 (100) $[M+NH_4^+]$, 262 $[M+H]^+$ (52).

(*S*)-3-(3-phenylpropanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 158



N-H-oxazolidin-2-one functionalised resin **2** (1.00g, 1.10 mmol/g, 1.10 mmol) sealed into IRORI kans was pre-swollen in DCM (300 mL) at room temperature. DMAP (671.5 mg, 5.5 mmol) was added as a solid, followed by DCC (2.269 g, 11.0 mmol) and finally 3-phenyl-propionic acid (1.651 g, 11.0 mmol). The vessel was then purged with nitrogen before heating at reflux for 16 hours. After this time, the reaction was cooled and the resin filtered and washed thoroughly with DMF, DCM and DCM / MeOH. The functionalised resin **157** was then dried thoroughly in a vacuum oven at 40 °C.

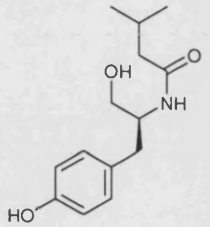
TFA cleavage: According to General procedure 8 (TFA cleavage) employing functionalised resin **157** (50 mg, 0.055 mmol), TFA cleavage solution (4 mL) **(*S*)-3-(3-phenylpropanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one 158** (14.3 mg, 0.044 mmol, 80%) was prepared as a white solid. m.p. 168 -169 °C; $[\alpha]_D^{21}$ + 114 ° (*c* 0.72, MeOH); ^{1}H NMR (d_4-MeOD, 300 MHz): δ 2.83 (1H, dd, *J* 13.5, 7.5 Hz, C*H*$_A$H$_B$Ar), 2.99 (2H, m, C*H*$_A$*H*$_B$Ph), 3.15 (1H, dd, *J* 13.5 7.0 Hz, CH$_A$*H*$_B$Ar), 3.30 (2H, m, COC*H*$_A$*H*$_B$), 4.25 (2H, m, C*H*$_2$O), 4.59 (1H, br. s, O*H*), 4.65 (1H, 1H, m, C*H*N), 6.72 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.96 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.17-7.33 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 31.8 (CH_2), 37.7 (CH_2), 38.7 (CH_2), 56.8 (CH), 68.0 (CH_2), 116.9 (CH), 127.6 (C), 127.7 (CH), 129.9 (CH), 130.0 (CH), 132.1 (CH), 142.6 (C), 155.9 (C=O), 158.2 (C), 174.4 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3401 (broad O-H), 1782 (C=O), 1683 (C=O); MS (CI+, NH_3) *m/z* (%) 343 (45) $[M+NH_4]^+$, 211 (100), 167 (90); HRMS (ES+) for $C_{19}H_{19}NO_4$ $[M+H]^+$ Calc. 326.1387, Found 326.1392.

General Procedure 8: TFA cleavage of auxiliary from resin.

A solution of DCM / TFA / TIS (94:1:5) (4 mL) was added *via* syringe to a dry round bottomed flask containing the functionalised resin (typically 20 mg). The flask was swirled

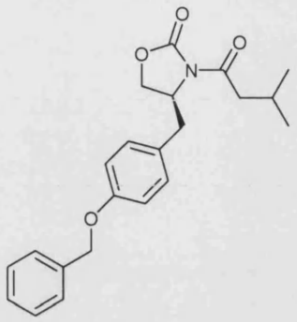
at 25 °C for 30 min. The resin was then filtered and washed thoroughly with DCM, THF and MeOH with all washings collected, combined and solvent removed *in vacuo*.

N-[2-hydroxy-1-(S)-(4-hydroxybenzyl)-ethyl]-3-methyl-butyramide, 161



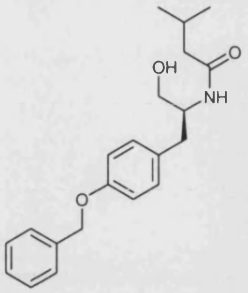
N-isovaleroyl-oxazolidin-2-one resin **151** (200 mg, 0.95 mmol/g, 0.19 mmol) preswollen in THF (10 mL) then LiOH (79.8 mg, 1.90 mmol) (in 2.0 mL H_2O) added and the reaction agitated on an orbital shaker for 6 hours. After this time, resin filtered and washed thoroughly (DCM, DCM / MeOH, THF) and dried in a vacuum oven at 40 °C. The resin then underwent TFA cleavage, according to General procedure 8, employing functionalised resin **160** (not shown) (200 mg, 0.19 mmol) and TFA cleavage solution (12 mL) to afford a crude mixture of products. Purification *via* column chromatography afforded ***N*-[2-hydroxy-1-(*S*)-(4-hydroxybenzyl)-ethyl]-3-methyl-butyramide 161** (12.4 mg, 0.05 mmol, 26%) as a colourless oil. $[\alpha]_D^{21}$ + 8.8 ° (*c* 0.225, MeOH); ^{1}H NMR (d_4-MeOD, 300 MHz): δ 0.71 (3H, d, *J* 6.5 Hz, C*H*$_3$), 0.76 (3H, d, *J* 6.5 Hz, C*H*$_3$), 1.75-1.92 (3H, br. m, COC*H*$_2$ and C*H*(CH$_3$)$_2$), 2.48 (1H, dd, *J* 13.5, 8.5 Hz, C*H*$_A$H$_B$Ar), 2.73 (1H, dd, *J* 13.5, 6.0 Hz, CH$_A$*H*$_B$Ar), 3.40 (2H, d, *J* 5.5 Hz, C*H*$_2$OH), 3.97 (1H, m, C*H*N), 4.90 (1H, br. s, N*H*), 6.59 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.94 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 23.0 (CH$_3$), 23.1 (CH$_3$), 27.8 (CH), 37.6 (CH$_2$), 46.9 (CH$_2$), 54.6 (CH), 64.9 (CH$_2$), 116.5 (CH), 131.0 (C), 131.6 (CH), 157.2 (C), 172.3 (C=O); IR (Thin film) ν_{max} (cm^{-1}): 3398 (broad O-H), 1665 (C=O); MS (CI+, NH_3) *m/z* (%) 252 (11) [M+H]$^+$, 52 (100); HRMS (ES+) for $C_{14}H_{21}NO_3$ [M+H]$^+$ Calc. 252.1594, Found 252.1595.

(*S*)-4-(4-Benzyloxy-benzyl)-3-(3-methyl-butyrl)-oxazolidin-2-one, 162



According to general procedure 3, lithium chloride (90.2 mg, 2.118 mmol), triethylamine (0.492 mL, 3.529 mmol) and isovaleric anhydride (0.599 mL, 3.00 mmol) were added to a *N*-H-oxazolidin-2-one **103** (500.0 mg, 1.765 mmol) in THF (15 mL) to afford crude **162**. Recrystallisation (ether, hexane) yielded **162** as a white solid (551 mg, 1.500 mmol, 85%). m. p. 96-98 °C; $[\alpha]_D^{21}$ + 48 ° (*c* 0.65, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.00 (3H, d, *J* 6.0 Hz, CH_3), 1.02 (3H, d, *J* 6.0 Hz, CH_3), 2.22 (1H, m, CH(CH_3)$_2$), 2.70 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH$_B$Ar), 2.77 (1H, dd, *J* 16.0, 7.0 Hz, CH_AH$_B$CO), 2.89 (1H, dd, *J* 16.0, 7.0 Hz, CH$_A$$H_B$CO), 3.23 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$$H_B$Ar), 4.16 (2H, m, C$H_2$O), 4.63 (1H, m, C$H$N), 5.04 (2H, s, ArOC$H_2$Ar), 6.93 (2H, app. d, *J* 8.5 Hz, *o*-OArH), 7.13 (2H, app. d, *J* 8.5 Hz, *m*-OArH), 7.32-7.45 (5H, br. m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.9 (CH_3), 23.0 (CH_3), 25.4 (CH), 37.5 (CH_2), 44.4 (CH_2), 55.6 (CH), 66.5 (CH_2), 70.4 (CH_2), 115.7 (CH), 127.9 (CH), 127.9 (C), 128.4 (CH), 129.0 (CH), 130.9 (CH), 137.3 (C), 153.9 (C=O), 158.5 (C), 173.1 (C=O); IR (KBr) ν_{max} (cm^{-1}): 1761 (C=O), 1706 (C=O); MS (CI+, NH_3) *m/z* (%) 385 (100) $[M+NH_4]^+$.

***N*-[(*S*)-1-(4-Benzyloxy-benzyl)-2-hydroxy-ethyl]-3-methyl-butyramide, 163**



Crude **163** isolated in 1:2 ratio with *N*H oxazolidin-2-one **103**. Not purified further.

^{1}H NMR (d_4-MeOD, 300 MHz): δ 0.73 (3H, d, *J* 6.5 Hz, C*H*$_3$), 0.79 (3H, d, *J* 6.5 Hz, C*H*$_3$), 1.80-1.95 (3H, br. m, C*H*$_2$C*H*(CH$_3$)$_2$), 2.54 (1H, dd, *J* 13.5, 8.5 Hz, CH$_A$H$_B$Ar), 2.78 (1H, dd, *J* 13.5, 6.0 Hz, CH$_A$*H*$_B$Ar), 3.41 (2H, d, *J* 5.5 Hz, C*H*$_2$OH), 4.01 (1H, m, C*H*N), 4.98 (2H, s, OC*H*$_2$Ar), 6.82 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.03 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.14-7.35 (5H, br. m, Ar*H*).

General procedure 9: LiOOH cleavage of solid-supported *N*-acyl-oxazolidin-2-ones.

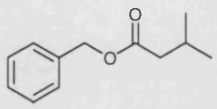
Functionalised resin (1 equiv.) placed loose in flask and preswollen in THF for 30 minutes before cooling to 0 °C. H_2O_2 (10 equiv.) added, followed by LiOH (5 equiv.) dissolved in a minimum volume of H_2O. The reaction was agitated on an orbital shaker for 4 hours, then the resin filtered off and washed thoroughly with DCM and THF. All washings were collected and evaporated to dryness. The residue was then redissolved in EtOAc and H_2O. The aqueous layer was acidified to pH 1 with 2.0 N HCl (aq.) and saturated by the addition of sodium chloride, before back-extracting into fresh EtOAc. The combined organic fractions were then dried with $MgSO_4$, filtered and solvent removed *in vacuo* to afford the acid product.

General Procedure 10: LiOBn cleavage of side chain from auxiliary

n-BuLi (5 equiv.) was added dropwise to a stirred solution of benzyl alcohol (6 equiv.) in THF at 0 °C. An aliquot of the resulting solution was removed *via* syringe and injected into a flask containing functionalised resin (1 equiv.) pre-swollen in THF, also at 0 °C. The

mixture was allowed to warm slowly to 25 °C and was stirred for 16 hours. The resin was then filtered and washed thoroughly with DCM and THF, with all washings collected, combined and solvent removed *in vacuo.*

3-methyl-butyric acid benzyl ester



According to general procedure 10, LiOBn was created *in situ* from *n*-BuLi (0.226 mL, 2.43 M, 0.55 mmol) and BnOH (0.683 mL, 0.66 mmol) in 2 mL THF, and added to *N*-isovaleryl-oxazolidin-2-one resin **151** (100 mg, 1.10 mmol/g, 0.11 mmol) in THF (5 mL) at 0 °C. The reaction was then agitated on an orbital shaker for a further 16 hours, allowing to warm slowly to room temperature. The resin was then filtered and washed thoroughly with DCM and THF, with all washings collected and the solvent removed *in vacuo* to afford crude **164** (contaminated with excess BnOH) as a pale yellow oil.

Purification Method 1 (column chromatography): Crude **164** passed though a pad of silica to afford pure **3-methyl-butyric acid benzyl ester 164** (16.7 mg, 0.09 mmol, 79%).

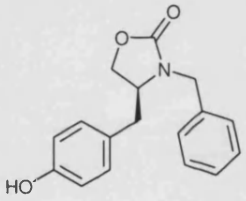
Purification Method 2 (Removal of excess BnOH *via* solid phase scavenging): Crude **164** redissolved in DCM and pyridine (2:1) (40 mL). ps-tosyl resin (3.437 g, 2.4 mmol/g, 8.25 mmol) added and the reaction agitated for 16 hours on an orbital shaker. After filtration of the resin and thorough washing with DCM, the organic layer was washed with 1.0N HCl (aq.) and brine and the solvent removed *in vacuo* to afford **3-methyl-butyric acid benzyl ester 164** (21.1 mg, 0.445 mL, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (6H, d, *J* 7.0 Hz, 2 x C*H*$_3$), 2.14 (1H, m, C*H*(CH_3)$_2$), 2.30 (2H, d, *J* 7.0 Hz, C*H*$_2$), 5.08 (2H, s, C*H*$_2$Ph), 7.14-7.36 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.8 (CH_3), 22.9 (CH_3), 25.6 (CH), 44.5 (CH_2), 66.4 (CH_2), 126.4 (CH), 127.8 (CH), 128.6 (CH), 136.6 (C), 178.7 (C=O). Spectroscopic data identical to literature compound. [115]

General procedure 11: $NaBH_4$ cleavage of solid-supported *N*-acyl-oxazolidin-2-ones.

Functionalised resin (1 equiv.) placed loose in flask and preswollen in THF. A solution of $NaBH_4$ (5 equiv.) in a minimum volume of H_2O was added and the reaction agitated on an orbital shaker for 4 hours. The resin was filtered off and washed thoroughly with DCM and THF, with all washings collected and evaporated to dryness. The residue was then redissolved in EtOAc and H_2O and extracted into EtOAc. The combined organic fractions were then dried with $MgSO_4$, filtered and solvent removed *in vacuo* to afford the alcohol product.

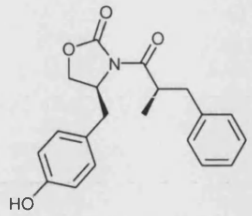
7.4 Compounds from Chapter 4

3-Benzyl-4-(4*S*)-(4-hydroxy-benzyl)-oxazolidin-2-one, 149



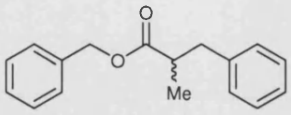
According to general procedure 1, using *N*-benzyl-oxazolidin-2-one **122** (100 mg, 0.267 mmol), Pd/C (10%) (14 mg, 0.014 mmol) and methanol / ethyl acetate (1:1, 10 mL) **149** was prepared as a colourless oil (66.6 mg, 0.235 mmol, 88%). $[\alpha]_D^{21}$ + 14° (*c* 0.7, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.51 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.92 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.69 (1H, m, C*H*N), 3.94 (1H, dd, *J* 8.5, 6.0 Hz, C*H*$_A$H$_B$O), 4.05 (2H, m, CH$_A$*H*$_B$O, NC*H*$_A$H$_B$), 4.80 (1H, d, *J* 15.0, NCH$_A$*H*$_B$), 6.71 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.82 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.16 – 7.33 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 37.8 (CH_2), 46.7 (CH_2), 55.8 (CH), 67.5 (CH_2), 116.3 (CH), 127.1 (C), 128.5 (CH), 128.6 (CH), 129.3 (CH), 130.5 (CH), 136.1 (C), 155.8 (C=O), 159.2 (C); IR (Thin film) ν_{max} (cm^{-1}): 3365 (broad O-H), 1742 (C=O); MS (CI+, NH_3) m/z (%) 301 (100) [M+NH_4^+], 284 (40) [M+H^+]; HRMS (ES+) for $C_{17}H_{17}NO_3$ [M+H]$^+$ Calc. 284.1281, Found 284.1278.

(4*S*)-4-(4-Hydroxy-benzyl)-3-((2*R*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 147



According to General procedure 1 using oxazolidin-2-one **115** (1.56 g, 3.64 mmol), Pd/C (10%) (192 mg, 0.18 mmol) and methanol/ ethyl acetate (1:1, 20 mL), **147** was prepared (1.03 g, 3.02 mmol, 83%) as a white solid. m. p. 142-143 °C; $[\alpha]_D^{21}$ + 79° (*c* 1.35, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (3H, d, *J* 7.0 Hz, C*H*$_3$), 2.44 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.58 (1H, dd, *J* 13.0, 7.5 Hz, CH(CH$_3$)*H*$_A$H$_B$), 2.83 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.06 (1H, dd, *J* 13.0, 7.0 Hz, CH(CH$_3$)H$_A$*H*$_B$), 4.03 (3H, m, C*H*$_A$*H*$_B$O, C*H*CH$_3$), 4.52 (1H, m, C*H*N), 5.83 (1H, br. s, O*H*), 6.65 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.75 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.06-7.19 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 17.3 (CH_3), 37.1 (CH_2), 40.1 (CH), 40.3 (CH_2), 55.6 (CH), 66.5 (CH_2), 116.3 (CH), 126.9 (C), 128.8 (CH), 129.6 (CH), 129.8 (CH), 131.0 (CH), 139.5 (C), 153.9 (C=O), 155.8 (C), 177.3 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3345 (O-H), 1771 (C=O), 1667 (C=O); MS (CI+, NH_3) m/z (%) 340 (100) [M+H$^+$], 357 (98) [M+NH$_4^+$]; HRMS (ES+) for $C_{20}H_{21}NO_4$ [M+H]$^+$ Calc. 340.1543, Found 340.1542.

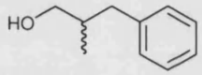
***rac*-Benzyl 2-benzylpropanoate, 168**



Benzyl alcohol (0.133 mL, 1.287 mmol) in THF (1 mL) was cooled to 0 °C and *n*-BuLi (0.429 mL, 2.5 M, 1.073 mmol) added dropwise. After stirring at 30 minutes, the entire reaction was transferred *via* cannula to a solution of oxazolidin-2-one **167** (100 mg, 0.429 mmol) in dry THF (3 mL), also at 0 °C. The resulting mixture was stirred for a further two hours at 0 °C and then quenched by addition of saturated ammonium chloride solution and extracted into EtOAc. The combined organic extracts were washed with 1N HCl (aq), brine, dried with $MgSO_4$, filtered and solvent removed *in vacuo*. Column chromatography

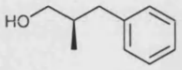
afforded ***rac*-Benzyl 2-benzylpropanoate *rac*-168** (46.2 mg, 0.182 mmol, 78%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, d, *J* 7.0 Hz, C*H*$_3$), 2.70 (1H, dd, *J* 13.0, 7.5 Hz, C*H*$_A$H$_B$Ph), 2.82 (1H, app. q, *J* 7.5 Hz, CH$_A$*H*$_B$Ph), 3.04 (1H, dd, *J* 13.0, 7.0 Hz, C*H*CH$_3$), 5.08 (2H, s, OC*H*$_2$Ph), 7.14-7.36 (10H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 17.3 (CH_3), 40.4 (CH), 42.0 (CH_2), 66.8 (CH_2), 126.8 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 129.0 (CH), 129.6 (CH), 136.5 (C), 139.9 (C), 176.5 (C=O).
Spectroscopic data identical to literature reference.[116]
HPLC conditions: ChiralCel OJ-R column, 60% acetonitrile, 40% water, 0.5 ml/min.
Enantiomer 1: t_R 15.7 min, Enantiomer 2: t_R 18.3 min.

***rac*-2-methyl-3-phenylpropan-1-ol, 169**



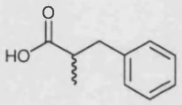
Sodium borohydride ($NaBH_4$) (35.2 mg, 0.932 mmol) in 1.5 mL H_2O was added dropwise to a solution of oxazolidin-2-one **167** (100mg, 0.233 mmol) in THF (2.5 mL) and stirred for 6 hours at room temperature. After this time the reaction was extracted into EtOAc (x3) and the combined organic layers washed with brine, dried with MgSO4, filtered and evaporated to dryness. Purification *via* column chromatography yielded ***rac*-2-methyl-3-phenylpropan-1-ol *rac*-169** (31.1 mg, 0.207 mmol, 89%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.84 (1H, br. s, O*H*), 1.95 (1H, m, C*H*CH$_3$), 2.41 (1H, dd, *J* 13.5, 8.5 Hz, C*H*$_A$H$_B$Ph), 2.75 (1H, dd, *J* 13.5, 8.0 Hz, CH$_A$*H*$_B$Ph), 3.50 (2H, m, C*H*$_2$OH), 7.18-7.29 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.5 (CH_3), 38.2 (CH), 39.6 (CH_2), 68.2 (CH_2), 126.4 (CH), 128.3 (CH), 129.2 (CH), 139.8 (C). Spectroscopic data identical to literature reference.[117]
HPLC conditions: ChiralCel OD column, 97% Hexane, 3% isopropyl alcohol, 1 ml/min, **(*S*)-169** t_R 10.3 min, **(*R*)-169** t_R 12.8 min.

2(*R*)-methyl-3-phenylpropan-1-ol, (*R*)-169 (major product of enolate alkylation employing *(S)*-**2**)



Spectroscopic data as for ***rac*-169** described above, except $[\alpha]_D^{21}$ + 12 ° (c 1.1, $CHCl_3$).

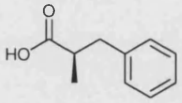
***rac*-2-benzylpropionic acid, *rac*-65**



(Commercially available product). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15 (3H, d, *J* 7.0 Hz, CH_3), 2.63 (1H, dd, *J* 13.5, 8.0 Hz, CH_AH_BPh), 2.73 (1H, m, C*H*), 3.05 (1H, dd, *J* 13.0, 8.0 Hz, CH_AH_BPh), 7.11-7.30 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.4 (CH_3), 40.1 (CH_2), 40.9 (CH), 126.3 (CH), 127.2 (CH), 128.8 (CH), 139.2 (C), 182.4 (C=O). Spectroscopic data identical to literature reference. [118]

HPLC conditions: ChiralCel OJ column, 98% *n*-Hexane, 2% isopropyl alcohol, 0.1% TFA, 1 ml/min. **(*R*)-65** t_R 9.5 min, **(*S*)-65** t_R 10.8 min.

2(*R*)-benzyl-propionic acid, (*R*)-65 (major product of enolate alkylation employing *(S)*-**2**)



Spectroscopic data as for ***rac*-65** described above, except $[\alpha]_D^{21}$ - 25 ° (*c* 1.0, $CHCl_3$);

General procedure 12: Solid phase enolate alkylation reaction – optimised method

Functionalised resin (150 mg, 1 equiv.) was sealed into an IRORI minikan and placed into an oven-dried round bottomed flask. THF (8 mL) was added to preswell the resin and the flask cooled to 0 °C. LHMDS (10 equiv., 1.0 M in THF) was added dropwise *via* syringe and the reaction was stirred for 30 minutes before the reaction solution was removed *via*

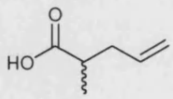
cannula. The resin was then resuspended in fresh, pre-chilled THF and treated with an electrophile (20 equiv.) before being stirred for a further 5 minutes at 0 °C, then removed from the icebath and stirred for a further 20 minutes. The reaction was quenched by the addition of pH 7 phosphate buffer solution, the IRORI kan immediately removed from the reaction solution *via* filtration, and the resin washed thoroughly using DCM, DCM / MeOH and THF in alternate cycles. TFA cleavage of 20 mg of the resulting resin was achieved according to general procedure 8, with the remaining approximately 130 mg resin cleaved *via* LiOOH hydrolysis, according to general procedure 9.

7.5 Compounds from Chapter 5

General procedure 13: Alkylation of acids.

Diisopropylamine in dry THF was cooled to 0 °C, and *n*-BuLi added dropwise. After 30 minutes, acid in dry THF solution was added dropwise over a period of 20 minutes. The resulting solution was stirred at 0 °C for 40 minutes before dropwise addition of the electrophile. The reaction was allowed to warm slowly to room temperature and stirred for 12 hours. The pH of the solution was adjusted to 2.5 with 2N HCl solution. The organic layer was separated and extracted with saturated sodium bicarbonate solution. The aqueous layer was acidified with 2N HCl solution to pH 2, saturated with sodium chloride, and extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over anhydrous MgSO4, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography.

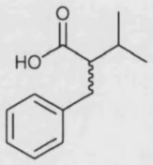
***rac*-2-methylpent-4-enoic acid, 181**



According to General procedure 13, propionic acid (0.373 mL, 5.0 mmol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 M, 10.5 mmol) and allyl iodide (0.549 ml, 6.0 mmol) to form ***rac*-2-methylpent-4-enoic acid 181** as a colourless oil (519 mg, 4.55 mmol, 91%). ^{1}H-NMR ($CDCl_3$, 300

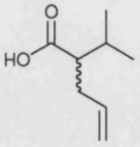
MHz): δ 1.17 (3H, d, *J* 7.0 Hz, CH_3), 2.16 (1H, m, CH_AH_B), 2.36 (1H, m, CH_AH_B), 2.50 (1H, m, $CHCH_3$), 5.01 (2H, m, $=CH_2$), 5.75 (1H, m, *H*C=); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 16.6 (CH_3), 37.8 (CH_2), 39.4 (CH), 117.5 (CH_2), 135.5 (CH), 182.5 (C=O). Spectroscopic data identical to literature compound. [119]

***rac*-2-benzyl-3-methylbutanoic acid, 182**



According to General procedure 13, isovaleric acid (0.552 mL, 5.0 mol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 M, 10.5 mmol) and benzyl bromide (0.714 mL, 6.0 mmol) to form ***rac*-2-isopropylpent-4-enoic acid 182** as a colourless oil (855 mg, 4.45 mmol, 89%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.05 (6H, m, CH_3), 1.91 (1H, m, $CH(CH_3)_2$), 2.45 (1H, m, $CHCH_2$), 2.80 (2H, br. d, *J* 6.5 Hz, CH_2), 7.10 - 7.24 (5H, br. m, Ph); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 20.3 (CH_3), 20.7 (CH_3), 30.8 (CH), 35.7 (CH_2), 54.6 (CH), 126.6 (CH), 128.8 (CH), 129.1 (CH), 140.0 (C), 180.5 (C=O). Spectroscopic data identical to literature compound.[120]

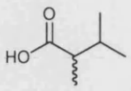
***rac*-2-isopropylpent-4-enoic acid, 183**



According to General procedure 13, isovaleric acid (0.552 mL, 5.0 mol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 M, 10.5 mmol) and allyl iodide (0.549 mL, 6.0 mmol) to form ***rac*-2-isopropylpent-4-enoic acid 183** as a colourless oil (590 mg, 4.15 mmol, 83%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.0 (6H, d, *J* 7.0 Hz, CH_3), 1.86 (1H, m, $CHMe_2$), 2.10 – 2.29 (3H, m, $CHCH_2$, CH_2), 5.03 (2H, m, $C=CH_2$), 5.76 (1H, m, *H*C=C); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 20.1

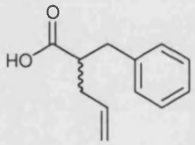
(CH_3), 20.2 (CH_3), 30.0 (CH), 33.6 (CH), 52.1 (CH_2), 116.7 (CH_2), 135.6 (CH), 180.5 (C=O). Spectroscopic data identical to literature compound. [121]

rac-2,3-dimethylbutanoic acid, 184



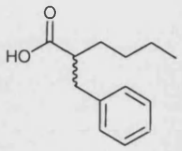
According to General procedure 13, isovaleric acid (0.552 mL, 5.0 mol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 M, 10.5 mmol) and methyl iodide (0.374 mL, 6.0 mmol) to form **_rac_-2,3-dimethylbutanoic acid 184** as a colourless oil (465 mg, 4.0 mmol, 80%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.92 (3H, d, *J* 7.0 Hz, C*H*$_3$), 0.97 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.10 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.89 (1H, m, C*H*(CH_3)$_2$), 2.29 (1H, m, C*H*CH_3); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 13.8 (CH_3), 19.6 (CH_3), 20.4 (CH_3), 30.6 (CH), 46.5 (CH), 181.3 (C=O).

rac-2-Allyl-3-phenylpropionic acid, 185



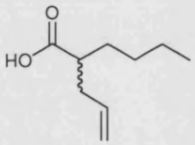
According to General procedure 13, phenylpropionic acid (750 mg, 5.0 mol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 M, 10.5 mmol) and allyl iodide (0.549 mL, 6.0 mmol) to form **_rac_-2-Allyl-3-phenylpropionic acid 185** as a colourless oil (856 mg, 4.50mmol, 90%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.29 – 2.46 (2H, m, C*H*$_2$CH=CH$_2$), 2.75 - 2.85 (2H, m, C*H*$_A$H$_B$Ph, C*H*CO), 2.97 - 3.05 (1H, m, CH$_A$*H*$_B$Ph), 5.08 - 5.15 (2H, m, C=C*H*$_2$), 5.74 - 5.88 (1H, m, *H*C=C), 7.19 – 7.34 (5H, m, Ph) 10.04 (1H, br. s, O*H*) ; ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 36.0 (CH_2), 37.7 (CH_2), 47.4 (CH), 117.9 (CH_2), 126.9 (CH), 128.9 (CH), 129.0 (CH), 129.3 (C), 135.1 (CH), 181.7 (C=O). Spectroscopic data identical to literature compound. [122]

***rac*-2-benzylhexanoic acid, 186**



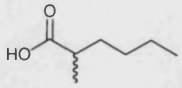
According to General procedure 13, hexanoic acid (0.627 mL, 5.0 mol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 M, 10.5 mmol) and benzyl bromide (0.714 mL, 6.0 mmol) to form ***rac*-2-benzylhexanoic acid 186** as a colourless oil (886 mg, 4.30 mmol, 86%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.82 (3H, m, CH_3), 1.22 – 1.68 (6H, br. m, $(CH_2)_3$), 2.62 (1H, m, C*H*), 2.75 (1H, dd, *J* 13.5, 9.0 Hz, CH_AH_BPh), 2.98 (1H, dd, *J* 13.5, 9.0 Hz, CH_AH_BPh), 7.11 – 7.29 (5H, br. m, *Ar*); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 13.5 (CH_3), 22.7 (CH_2), 27.5 (CH_2), 31.5 (CH_2), 39.3 (CH_2), 48.2 (CH), 126.6 (CH), 128.6 (CH), 129.0 (CH), 140.3 (C), 182.1 (C=O). Spectroscopic data identical to literature. [123]

***rac*-2-Allyl-hexanoic acid, 187**



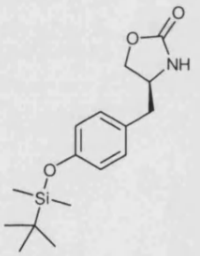
According to General procedure 13, hexanoic acid (0.627 mL, 5.0 mmol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 m, 10.5 mmol) and allyl iodide (0.549 mL, 6.0 mmol) to form ***rac*-2-Allyl-hexanoic acid 187** as a colourless oil (640 mg, 4.10 mmol, 82%). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.82 (3H, m, CH_3), 1.19–1.62 (6H, br. m, $(CH_2)_3$), 2.14-2.42 (3H, m, $CHCH_AH_BCH{=}CH_2$), 4.98 (2H, m, $=CH_2$), 5.74 (1H, m, $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.2 (CH_3), 22.9 (CH_2), 29.7 (CH_2), 31.6 (CH_2), 36.5 (CH_2), 45.5 (CH), 117.3 (CH_2), 135.6 (CH), 181.9 (C=O). Spectroscopic data identical to literature compound. [124]

***rac*-2-methylhexanoic acid, 188**



According to General procedure 13, hexanoic acid (0.627 mL, 5.0 mmol) was treated with LDA (formed *in situ* from diisopropylamine (1.472 mL, 10.5 mmol) and *n*-BuLi (4.20 mL, 2.5 m, 10.5 mmol) and methyl iodide (0.374 mL, 6.0 mmol) to form ***rac*-2-methylhexanoic acid 188** as a colourless oil (514 mg, 3.95 mmol, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (3H, m, CH_3), 1.11 (3H, d, *J* 7.0 Hz, CH_3), 1.25-1.70 (6H, br. m, (CH_2)$_3$), 2.65 (1H, m, C*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.7 (CH_3), 14.2 (CH_3), 20.4 (CH_2), 23.0 (CH_2), 27.9 (CH_2), 48.6 (CH), 181.8 (C=O). Spectroscopic data identical to literature compound.[125]

(*S*)-4-[4-(*tert*-Butyl-dimethyl-silanyloxy)-benzyl]-oxazolidin-2-one, 179



N-H-oxazolidin-2-one (966 mg, 5.0 mmol) **1** was dissolved in dry DMF (75 mL) and stirred at room temperature. Imidazole (851 mg, 12.5 mmol) TBDMS-Cl (1.130g, 7.5 mmol) and DMAP (122 mg, 1 mmol) were added sequentially to the reaction mixture and the reaction stirred for 8 hours. After this time the reaction was quenched with saturated ammonium chloride solution, and extracted into ether (x3). The combined organic extracts were then washed with saturated sodium bicarbonate, brine, dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting white solid was recrystallised (EtOAc, hexane) to afford **(*S*)-4-[4-(*tert*-Butyl-dimethyl-silanyloxy)-benzyl]-oxazolidin-2-one 179** as white needles. m.p. 102-104 °C; $[\alpha]_D^{21}$ - 48 ° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.19 (6H, s, SiCH_3), 0.98 (9H, s, C(CH_3)$_3$), 2.79 (2H, app. d, *J* 7.0 Hz, CH_2Ar), 4.03 (1H, m, C*H*N), 4.13 (1H, dd, *J* 8.5, 5.5 Hz, CH_AH$_B$O), 4.44 (1H, app. t, *J* 8.5 Hz, CH$_A$$H_B$O), 5.41 (1H, br. s, N*H*), 6.80 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.02 (2H, app. d, *J*

8.5 Hz, *m*-OAr*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ -4.0 (CH_3), 18.6 (C), 26.0 (CH_3), 41.1 (CH_2), 54.3 (CH), 70.1 (CH_2), 120.9 (CH), 128.9 (C), 130.3 (CH), 155.3 (C=O), 159.6 (C); IR (KBr) ν_{max} (cm^{-1}): 3140 (broad N-H), 1730 (C=O); HRMS (+ESI) for $C_{16}H_{25}NO_3Si$ $[M+H]^+$ Calc. 308.1682, Found 308.1694.

General procedure 14: Acylation of protected oxazolidin-2-one.

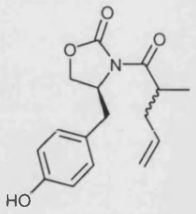
i) A solution of acid (2.0 mmol) in DCM (8 mL) was cooled to 0 °C and oxalyl chloride (2.0 mmol) added dropwise. The reaction mixture was refluxed for 2 hours then concentrated *in vacuo* to give the crude acyl chloride as a viscous oil.

ii) A solution of protected oxazolidin-2-one (1.0 mmol) in dry THF (8 mL) was cooled to -78 °C then *n*-BuLi (1.1 mmol) added dropwise. After the mixture was stirred for 30 minutes, the above acyl chloride dissolved in dry THF (5 mL) was added dropwise. The resulting mixture was stirred for 2 hours at -78 °C, then quenched with saturated ammonium chloride and partitioned between ether and water. The combined ether extracts were washed with saturated sodium bicarbonate and brine, dried with $MgSO_4$, filtered and evaporated *in vacuo*.

General Procedure 15: Removal of TBS-protecting group

N-acyl-oxazolidin-2-one (1 equivalent) was dissolved in THF and tetrabutylammonium fluoride (TBAF) (1.2 equivalents) added dropwise. The reaction was stirred at room temperature for 30 mins, before being quenched with saturated ammonium chloride and extracted into ether. The combined ether extracts were washed with brine, dried with MgSO4, filtered and evaporated *in vacuo*. Where necessary, the resulting residue was filtered through a plug of silica to remove any remaining TBAF residues.

(*S*)-3-(2-methylpent-4-enoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 194

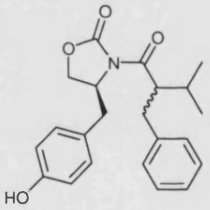


According to General Procedure 14, i) Acid **181** (228 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **179** (307 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the *N*-acyl-*O*-TBS-protected intermediate (not shown).

This residue was immediately treated according to General procedure 15, using TBAF (1.2 ml, 1.2 mmol) in THF (10 mL), to afford the crude product which was filtered through a plug of silica to afford **(*S*)-3-(2-methylpent-4-enoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 194** (185 mg, 0.64 mmol, 64%).

HPLC conditions could not be found that would resolve the two diastereomers.

(*S*)-3-(2-benzyl-3-methylbutanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 195

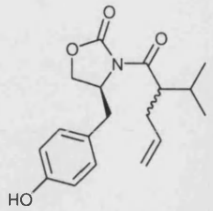


According to General Procedure 14, i) Acid **182** (385 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **103** (283 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the *N*-acyl-*O*-Bn-protected intermediate (not shown).

This residue was immediately treated according to General procedure 1, using Pd / C (10%) (50 mg) in MeOH / EtOAc (1:1) (15 mL), to afford **(*S*)-3-(2-benzyl-3-methylbutanoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 195** (257 mg, 0.70mmol, 70%).

HPLC conditions: ChiralCel AD column, 95% *n*-Hexane, 5% Isopropyl alcohol, 1.0 ml / min. **(*S,R*)-195** (minor diastereomer) t_R 32.4min. **(*S,S*)-195** (major diastereomer) t_R 37.0 min.

(*S*)-3-(2-isopropylpent-4-enoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 196

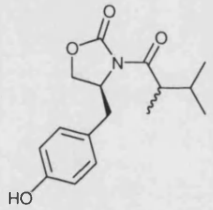


According to General Procedure 14, i) Acid **183** (284 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **179** (307 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the *N*-acyl-*O*-TBS protected intermediate (not shown).

This residue was immediately treated according to General procedure 15, using TBAF (1.2 ml, 1.2 mmol) in THF (10 mL), to afford the crude product, which was filtered through a plug of silica to afford **(*S*)-3-(2-isopropylpent-4-enoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 196** (209 mg, 0.66 mmol, 66%).

HPLC conditions: ChiralCel AD column, 97% n-Hexane, 3% Isopropyl alcohol, 0.6 ml / min. **(*S,R*)-196** (minor diastereomer) t_R 60.9 min. **(*S,S*)-196** (major diastereomer) t_R 66.5 min.

(*S*)-3-(2,3-dimethylbutanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 197

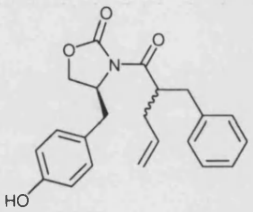


According to General Procedure 14, i) Acid **184** (232 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **103** (283 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the *N*-acyl-*O*-Bn protected intermediate (not shown).

This residue was immediately treated according to General procedure 1, using Pd / C (10%) (50 mg) in MeOH / EtOAc (1:1) (15 mL), to afford **(*S*)-3-(2,3-dimethylbutanoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 197** (218 mg, 0.75 mmol, 75%).

HPLC conditions: ChiralCel OD column, 97% *n*-Hexane, 3% Isopropyl alcohol, 1.0 ml / min. **(*S,S*)-197** (major diastereomer) t_R 73.4 min. **(*S,R*)-197** (minor diastereomer) t_R 84.6 min.

(*S*)-3-(2-benzylpent-4-enoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 198

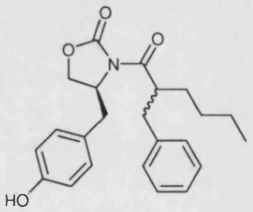


According to General Procedure 14, i) Acid **185** (380 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **179** (307 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the *N*-acyl-*O*-TBS-protected intermediate (not shown).

This residue was immediately treated according to General procedure 15, using TBAF (1.2 ml, 1.2 mmol) in THF (10 mL), to afford the crude product which was filtered through a plug of silica to afford **(*S*)-3-(2-benzylpent-4-enoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 198** (263 mg, 0.72 mmol, 72%).

HPLC conditions: ChiralCel AD column, 99% *n*-Hexane, 1% Isopropyl alcohol, 0.6 ml / min. Diastereomer 1 t_R 26.1 min. Diastereomer 2 t_R 29.6 min. (Due to unknown impurity dominating HPLC spectra, it could not be determined which peak corresponded to the major diastereomer).

(*S*)-3-(2-benzylhexanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 199



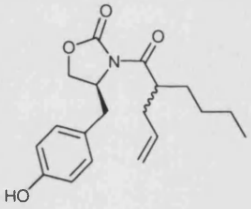
According to General Procedure 14, i) Acid **186** (412 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **103** (283 mg, 1.0

mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the *N*-acyl-*O*-Bn-protected intermediate (not shown).

This residue was immediately treated according to General procedure 1, using Pd / C (10%) (50 mg) in MeOH / EtOAc (1:1) (15 mL), to afford **(*S*)-3-(2-benzylhexanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one 199** (250 mg, 0.66 mmol, 66%).

HPLC conditions: ChiralCel OD column, 95% *n*-Hexane, 5% Isopropyl alcohol, 1.0 mL / min. **(*S,S*)-199** (minor diastereomer) t_R 37.5 min. **(*S,R*)-199** (major diastereomer) t_R 44.8 min.

(*S*)-3-(2-allylhexanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 200

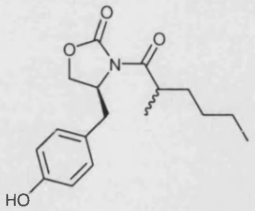


According to General Procedure 14, i) Acid **187** (412 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **179** (307 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the N-acyl-O-TBS-protected intermediate, (not shown).

This residue was immediately treated according to General procedure 15, using TBAF (1.2 ml, 1.2 mmol) in THF (10 mL), to afford the crude product which was filtered through a plug of silica to afford **(*S*)-3-(2-allylhexanoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 200** (225 mg, 0.68 mmol, 68%).

HPLC conditions: ChiralCel AD column, 97% *n*-Hexane, 3% Isopropyl alcohol, 1.0 ml / min. **(*S,R*)-200**(major diastereomer) t_R 35.0 min, **(*S,S*)-200** (minor diastereomer) t_R 39.9 min.

(*S*)-3-(2-methylhexanoyl)-4-(4-hydroxybenzyl)-oxazolidin-2-one, 201

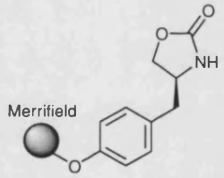


According to General Procedure 14, i) Acid **188** (260 mg, 2.0 mmol) in DCM treated with oxalyl chloride (0.174 mL, 2.0 mmol) and ii) *N*-H-oxazolidin-2-one **103** (283 mg, 1.0 mmol) was treated with *n*-BuLi (0.44 mL, 2.5 M, 1.1 mmol) in dry THF to form the N-acyl-O-Bn-protected intermediate (not shown).

This residue was immediately treated according to General procedure 1, using Pd / C (10%) (50 mg) in MeOH / EtOAc (1:1) (15 mL), to afford **(*S*)-3-(2-methylhexanoyl)-4-(4-hydroxybenzyl)oxazolidin-2-one 201** (218 mg, 0.72 mmol, 72%).

HPLC conditions: ChiralCel AD column, 99% *n*-Hexane, 1% Isopropyl alcohol, 0.7 ml / min. **(*S,S*)-201** (major diastereomer) t_R 133.4 min, **(*S,R*)-201** (minor diastereomer) t_R 146.5 min.

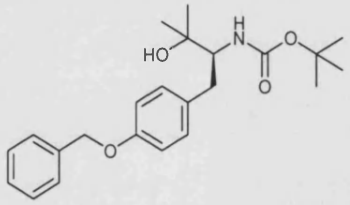
Merrifield-supported *N*-H-oxazolidin-2-one, 72a



Merrifield resin (1.00g, 1.26 mmol) was preswollen in DMF (100 mL) at ambient temperature. 18-crown-6 (large crystal) and potassium carbonate (522 mg, 3.78 mmol) were added and the reaction vessel purged with nitrogen. Finally, a solution of *N*-H-oxazolidin-2-one **1** (730 mg, 3.78 mmol) in DMF was added *via* syringe and the reaction heated at 60 °C for 18 hours. After this time, the reaction was cooled to ambient temperature and the resin removed *via* filtration. The resin was washed thoroughly with DCM, THF and DCM / MeOH, with all washings collected. In order to recover the excess oxazolidin-2-one fragment, the combined washings were evaporated to dryness, redissolved in methanol and passed through a solid phase extraction column (SCX-2) with the resulting

filtrate evaporated to yield pure oxazolidin-2-one. Meanwhile, the resin was dried thoroughly in a vacuum oven at 40 °C. The loading of the resin was determined *via* gravimetric analysis of the resulting resin and comparison with the original mass of resin employed in the reaction. In this way the resin loading was calculated as 0.95 $mmolg^{-1}$ (75%).

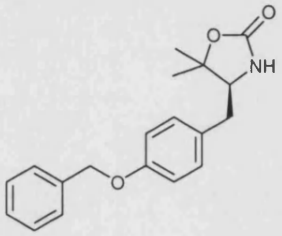
tert-butyl 1-(4-(benzyloxy)phenyl)-3-hydroxy-3-methylbutan-2-ylcarbamate, 215



A large 3-necked flask fitted with a reflux condenser and thermometer was charged with magnesium turnings (1.684 g, 69.30 mmol) and flushed with nitrogen. Diethyl ether (20 mL) was added *via* cannula and the whole slowly stirred. In order to initiate the reaction, approximately 0.5 mL of iodomethane was added dropwise until the reaction was refluxing gently. The remainder of the iodomethane (in total, 4.314 mL, 69.30 mmol) was diluted in diethyl ether (40 mL) and added dropwise over 30 mins so as to maintain a gentle reflux. The newly formed solution of the Grignard reagent was then allowed to cool to room temperature before careful addition of a solution of ester **106** (7.996 g, 17.324 mmol) in THF (40 mL), again added dropwise so as to maintain a gentle reflux. After addition was complete, the reaction was allowed to stir at room temperature for a further 4 hrs. The reaction was quenched by careful addition of a saturated solution of potassium sodium tartrate, forming a pale grey, granular precipitate which was filtered through a pad of celite. The precipitate was washed with diethyl ether, and the filtrate evaporated to yield **215** as a white powder (5.009 g, 12.993 mmol, 75%). m. p. 138-139°C; $[\alpha]_D^{21}$ - 39° (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (9H, s, Boc-C*H*$_3$), 1.30 (6H, s, C(OH)(C*H*$_3$)$_2$), 2.54 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.02 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.64 (1H, m, C*H*N), 4.6 (1H, d, *J* 9.5 Hz, N*H*), 5.03 (2H, s, OC*H*$_2$Ar), 6.89 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.10 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.27-7.44 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 26.9 (CH_3), 27.9 (CH_3), 28.7 (CH_3), 35.5 (CH_2),

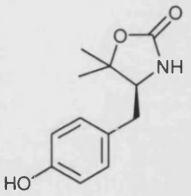
60.9 (CH), 70.4 (CH_2), 73.3 (C), 79.6 (C), 115.2 (CH), 127.8 (CH), 128.3 (CH), 128.9 (CH), 130.5 (CH), 131.7 (C), 137.7 (C), 156.9 (C), 157.7 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3493 (broad O-H), 3379 (broad N-H), 1669 (C=O); MS (CI+, NH_3) *m/z* (%) 386 (88) $[M+H]^+$, 347 (100), 330 (96); HRMS (ES+) for $C_{23}H_{31}NO_4[M+H]^+$ Calc. 386.2326, Found 386.2328.

(*S*)-4-(4-(benzyloxy)benzyl)-5,5-dimethyloxazolidin-2-one, 216



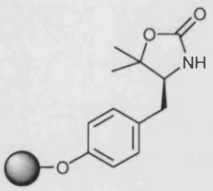
A suspension of sodium hydride (0.788 g, 32.84 mmol) in THF (100 mL) was stirred at room temperature. A solution of alcohol **215** (4.220 g, 10.95 mmol) in THF (50 mL) was added dropwise and the reaction heated at 50 °C for 18 hrs. After this time, the reaction was allowed to cool, quenched with satd. NH_4Cl solution and extracted into ethyl acetate (x3). The combined organic fractions were washed with 1N HCl, satd. $NaHCO_3$ and brine, dried ($MgSO_4$) and solvent removed *in vacuo* to yield crude product. Recrystallisation (petroleum ether 40-60°C, ethyl acetate) produced oxazolidin-2-one **216** (2.727 g, 8.76 mmol, 80%) as pale yellow needles. m. p. 132-133°C; $[\alpha]_D^{21}$ - 83° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (6H, s, C*H*$_3$), 2.53 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.65 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ar), 3.55 (1H, dd, *J* 9.5, 4.0 C*H*N), 4.93 (2H, s, OC*H*$_2$Ar), 5.41 (1H, s, N*H*), 6.83 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.99 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.18-7.34 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.3 (CH_3), 28.0 (CH_3), 36.6 (CH_2), 63.6 (CH), 70.4 (CH_2), 83.7 (C), 115.8 (CH), 127.9 (CH), 128.4 (CH), 129.0 (CH), 129.6 (C), 130.3 (CH), 137.3 (C), 158.3 (C=O), 158.7 (C); IR (KBr) ν_{max} (cm^{-1}): 3417 (broad N-H), 1778 (C=O), 1715 (C=O); MS (CI+, NH_3) *m/z* (%) 329 (100) $[M+NH_3]^+$, 312 (58); HRMS (ES+) for $C_{19}H_{21}NO_3$ $[M+NH_4]^+$ Calc. 329.1860, Found 329.1861.

(*S*)-4-(4-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one, 217



According to General procedure 1 using SuperQuat oxazolidin-2-one **216** (2.600g, 8.350 mmol), Pd/C (10%) (440 mg, 0.418 mmol) and methanol/ ethyl acetate (1:1, 60 mL), **217** was prepared (1.755 g, 7.932 mmol, 94%) as cream coloured needles. m.p.139-140 °C; $[\alpha]_D^{21}$ -65° (*c* 1.00, EtOH); ^{1}H NMR (d_4-MeOD, 300 MHz): δ 1.24 (3H, s, C*H*$_3$), 1.28 (3H, s, C*H*$_3$), 2.55 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.67 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ar), 3.68 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 6.66 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.96 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 22.5 (CH_3), 28.3 (CH_3), 37.4 (CH_2), 64.9 (CH), 85.6 (C), 117.0 (CH), 129.8 (C), 131.6 (CH), 157.7 (C=O), 161.4 (C); IR (KBr) ν_{max} (cm^{-1}): 3430 (broad N-H), 1779 (C=O), 1718 (C=O); MS (CI+, NH_3) *m/z* (%) 239 (100) $[M+NH_3]^+$, 222 (53) $[M+H]^+$; HRMS (ES+) for $C_{12}H_{15}NO_3$ $[M+NH_4]^+$ Calc. 239.1390, Found 239.1390.

Immobilisation of phenolic SuperQuat-oxazolidin-2-one 217 onto 2-chlorotrityl-chloride resin to form 218

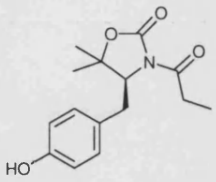


According to general procedure 6, 2-chlorotrityl-chloride resin (1.000 g, 1.20 mmolg^{-1}, 1.20 mmol) preswollen in DCM / THF (200 mL) was treated with *N*-H-SuperQuat-oxazolidin-2-one **217** (796.4 mg, 3.60 mmol) and diisopropylethylamine (2.090 mL, 12.0 mmol) to afford polymer-supported *N*-H-SuperQuat-oxazolidin-2-one **218**.

According to General Procedure 8, resin **218** (50 mg, 0.060 mmol) was treated with TFA cleavage solution (4 mL) to afford *N*-H-SuperQuat-oxazolidin-2-one **217** (11.7 mg, 0.053

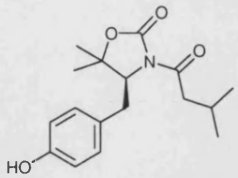
mmol). This indicated a resin loading of 1.06 mmolg^{-1} (88%, based on original loading of resin).

(*S*)-4-(4-hydroxybenzyl)-5,5-dimethyl-3-propionyloxazolidin-2-one, 219



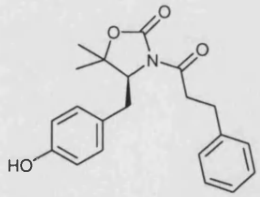
According to General Procedure 7, *N*H-SuperQuat-functionalised resin (500 mg, 1.06 mmol/g, 0.53 mmol) was treated with triethylamine (0.369 mL, 2.65 mmol) and propionic anhydride (0.340 mL, 2.65 mmol) to afford *N*-propionyl-SuperQuat-functionalised resin. Resin then cleaved according to general procedure 8 (TFA cleavage) in which functionalised resin **218** (50 mg, 0.106 mmol) was treated with TFA cleavage solution (4 mL) to afford **(*S*)-4-(4-hydroxybenzyl)-5,5-dimethyl-3-propionyloxazolidin-2-one 219** as a colourless oil (27 mg, 0.098 mmol, 92%). $[\alpha]_D^{21}$ -40 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, d, *J* 7.0 Hz, CH_2CH_3), 1.38 (3H, s, CH_3), 1.39 (3H, s, CH_3), 2.85 (1H, dd, *J* 14.0, 9.5 Hz, CH_AH_BAr), 2.91 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.04 (1H, dd, *J* 14.0 Hz, 4.0 Hz, CH_AH_BAr), 4.42 (1H, dd, *J* 9.5, 4.0 Hz, CHN), 6.77 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 7.12 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 8.9 (CH_3), 22.8 (CH_3), 29.2 (CH_3), 29.8 (CH_2), 35.6 (CH_2), 63.9 (CH), 83.8 (C), 116.4 (CH), 129.3 (C), 131.6 (CH), 153.2 (C=O), 161.7 (C), 173.8 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3310 (broad O-H), 1772 (C=O), 1709 (C=O); MS (CI+, NH_3) *m/z* (%) 295 (100) [M+NH_4^+], 278 (56) [M+H^+].

(*S*)-3-(3-methylbutanoyl)-4-(4-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one, 220



According to General Procedure 7, *N*H-SuperQuat-functionalised resin **218** (500 mg, 1.06 $mmolg^{-1}$, 0.53 mmol) was treated with triethylamine (0.370 mL, 2.65 mmol) and isovaleric anhydride (0.530 mL, 2.65 mmol) to afford *N*-isovaleryl-SuperQuat-functionalised resin. Resin then cleaved according to general procedure 8 (TFA cleavage) in which functionalised resin (50 mg, 0.106 mmol) was treated with TFA cleavage solution (4 mL) to afford **(*S*)-3-(3-methylbutanoyl)-4-(4-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one 220** as a colourless oil (29.1 mg ,0.095 mmol, 90%). $[\alpha]_D^{21}$ - 57 ° (*c* 1.2, $CHCl_3$); ^{1}H NMR (d_4-MeOD, 300 MHz): δ 0.81 (6H, d, *J* 6.5 Hz, $(CH_3)_2$), 1.22 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.98 (1H, m, $CH(CH_3)_2$), 2.61 (2H, m, $COCH_2$), 2.81 (2H, m, CH_AH_BAr), 4.40 (1H, dd, *J* 9.5, 4.0 Hz, CHN), 6.61 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.98 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 22.7 (CH_3), 22.9 (CH_3), 23.0 (CH_3), 25.4 (CH), 29.2 (CH_3), 36.8 (CH_2), 44.8 (CH_2), 64.2 (CH), 84.2 (C), 115.8 (CH), 129.0 (C), 131.4 (CH), 153.9 (C=O), 156.3 (C), 175.0 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3389 (broad O-H), 1760 (C=O), 1705 (C=O); MS (CI+, NH_3) *m/z* (%) 323 (87) [$M+NH_4^+$], 278 (32) [$M+H^+$].

(*S*)-3-(3-phenylpropanoyl)-4-(4-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one, 221



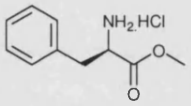
*N*H-SuperQuat-functionalised resin **218** (500 mg, 1.06 mmol/g, 0.53 mmol), sealed into IRORI mini-Kans ™ was preswollen in DCM at room temperature. DMAP (323.8 mg, 2.65 mmol) and hydrocinnamic acid (796.0 mg, 5.3 mmol) followed by DCC (1.094 g, 5.3 mmol) and the reaction heated at reflux for 16 hours. After this time, the reaction was

quenched by addition of saturated ammonium chloride solution and the resin removed *via* filtration. The resin was then washed thoroughly with DCM, DMF and DCM / MeOH, before being dried thoroughly in a vacuum oven at 40 °C.

The functionalised resin was then cleaved according to general procedure 8 (TFA cleavage) in which functionalised resin (50 mg, 0.106 mmol) was treated with TFA cleavage solution (4 mL) to afford **(*S*)-3-(3-phenylpropanoyl)-4-(4-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one 221** as a colourless oil (31.8 mg, 0.090 mmol, 85%). $[\alpha]_D^{21}$ -36 ° (*c* 1.1, $CHCl_3$); ^{1}H NMR (d_4-MeOD, 300 MHz): δ 1.29 (3H, s, CH_3), 1.30 (3H, s, CH_3), 2.58 (1H, dd, *J* 14.0, 9.5 Hz, CH_AH$_B$Ar), 2.65 – 2.98 (3H, br. m, CH_2Ph, CH$_A$$H_B$Ar), 3.06 (2H, m, COC$H_A$$H_B$), 4.38 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 6.61 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.95 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.02-7.20 (5H, br. m, Ar*H*); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 22.4 (CH_3), 28.8 (CH_3), 31.8 (CH_2), 35.4 (CH_2), 37.8 (CH_2), 62.8 (CH), 84.0 (C), 115.6 (CH), 127.6 (C), 127.7 (CH), 129.3 (C), 129.9 (CH), 130.0 (CH), 132.2 (CH), 154.2 (C=O), 158.3 (C), 173.8 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3398 (broad O-H), 1780 (C=O), 1692 (C=O); MS (CI+, NH_3) *m/z* (%) 371 (100) [M+NH_4^+], 354 (50) [M+H^+].

7.6 Compounds from Chapter 6

(*R*)-methyl 2-amino-3-phenylpropanoate hydrochloride, (*R*)-251

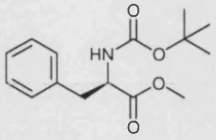


Thionyl chloride (13.247 mL, 181.6 mmol) was added dropwise to a stirred suspension of D-phenylalanine (20.00g, 121 mmol) in methanol (240 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 24 hours, after which time the solvent was removed *in vacuo* to give **(*R*)-methyl 2-amino-3-phenylpropanoate hydrochloride (*R*)-251** in quantitative yield. ^{1}H NMR (D_2O, 300 MHz): δ 3.17 (2H, m, CH_2), 3.70 (3H, s, CH_3), 4.33 (1H, app. t, *J* 4.3 Hz, C*H*N), 7.12-7.33 (5H, m, Ar-*H*). Spectroscopic data identical to literature compound.[126]

(*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride, (*S*)-251

Identical method but employing L-phenylalanine. Identical spectroscopic data.

***tert*-butyl (*R*)-1-(methoxycarbonyl)-2-phenylethylcarbamate, 252**

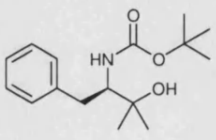


Solid sodium hydrogen carbonate (30.494 g, 363 mmol) was added in one portion to a stirred solution of **(*R*)-251** (21.685 g, 121 mmol) in ethanol (300 mL) at 0 °C, immediately followed by addition of solid boc anhydride (27.740 g, 127.1 mmol) in one portion. The reaction was allowed to warm to room temperature and stirred for 48 hours, after which the reaction was filtered through celite, washed with diethyl ether and evaporated. The resulting residue was redissolved in diethyl ether, filtered through celite again, washed with ether and evaporated to afford ***tert*-butyl (*R*)-1-(methoxycarbonyl)-2-phenylethylcarbamate (*R*)-252** (31.771 g, 113.7 mmol, 94%) as a colourless oil which solidified with time. m.p. 42-43 °C; $[\alpha]_D^{21}$ -38 ° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (9H, s, Boc-H), 3.08 (2H, m, CH_AH_BPh), 3.72 (3H, s, OCH_3), 4.59 (1H, m, C*H*N), 4.98 (1H, d, *J* 6.0 Hz, N*H*), 7.11-7.32 (5H, br. m, Ar-*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.5 (CH_3), 38.2 (CH_2), 52.0 (CH_3), 54.2 (CH), 80.3 (C), 127.4 (CH), 128.4 (CH), 129.3 (CH), 137.0 (C), 156.2 (C=O), 172.6 (C=O). Spectroscopic data identical to literature compound.[127]

***tert*-butyl (*S*)-1-(methoxycarbonyl)-2-phenylethylcarbamate, (*S*)-252**

Identical method but employing **(*S*)-251**, 92% yield, $[\alpha]_D^{21}$ + 40 ° (*c* 1.0, $CHCl_3$).

***tert*-butyl (*R*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate, (*R*)-253**



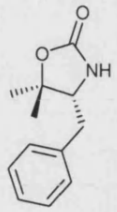
According to literature method of Bull *et al.*[82] a large 3-necked flask fitted with a reflux condenser and thermometer was charged with magnesium turnings (5.881 g, 242.0 mmol) and flushed with nitrogen. Diethyl ether (60 mL) was added *via* syringe. In order to

initiate the reaction, approximately 2 mL of iodomethane was added dropwise until the reaction was refluxing gently. The remainder of the iodomethane (in total, 15.066 mL, 242.0 mmol) was diluted in diethyl ether (120 mL) and added dropwise over 1 hour so as to maintain a gentle reflux. The newly formed solution of the Grignard reagent was then allowed to cool to room temperature before careful addition of a solution of ester **(*R*)-252** (16.899 g, 60.5 mmol) in THF (60 mL), again added dropwise so as to maintain a gentle reflux. After addition was complete, the reaction was allowed to stir at room temperature for a further 40 hrs. The reaction was quenched by careful addition of a saturated solution of potassium sodium tartrate, forming a pale grey, granular precipitate which was filtered through a pad of celite. The precipitate was washed with diethyl ether, and the filtrate evaporated to yield **(*R*)-253** as a white powder (14.188 g, 50.8 mmol, 84%). m. p. 101-103°C; $[\alpha]_D^{21}$ + 45 ° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (9H, s, boc-C*H*$_3$), 1.23 (6H, s, C(OH)(C*H*$_3$)$_2$), 2.53 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ph), 3.02 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ph), 3.62 (1H, m, C*H*N), 4.49 (1H, d, *J* 9.0, N*H*), 7.09-7.24 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 26.9 (CH_3), 27.8 (CH_3), 28.6 (CH_3), 36.4 (CH_2), 60.8 (CH), 73.4 (C), 79.6 (C), 126.5 (CH), 128.6 (CH), 129.5 (CH), 139.4 (C), 156.8 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3475 (broad O-H), 3379 (broad N-H), 1662 (C=O); MS (CI+, NH_3) *m/z* (%) 280 (100) $[M+H]^+$, 224 (100); HRMS (ES+) for $C_{16}H_{25}NO_3$ $[M+H]^+$ Calc. 280.1907, Found 280.1911.

***tert*-butyl (*S*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate, (*S*)-253**

Identical method but employing **(*S*)-253**, 86% yield, $[\alpha]_D^{21}$ - 45° (*c* 1.00, $CHCl_3$)

(*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one, (*R*)-211

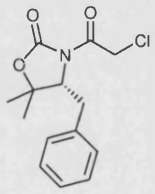


According to the literature method of Bull *et al.*, a solution of alcohol **(*R*)-253** (6.200 g, 22.192 mmol) in THF (150 mL) was cooled to 0 °C. Potassium *tert*-butoxide (2.739 g, 24.411 mmol) was added as one portion and the resulting suspension stirred for a further 30 mins until a yellow solution had been formed. The solvent was then removed *in vacuo* and the residue re-dissolved in ethyl acetate, washed with brine, dried ($MgSO_4$) and evaporated to give crude oxazolidin-2-one as a pale yellow solid. Recrystallisation (petroleum ether 40-60°C, ethyl acetate) yielded **(*R*)-211** as a white solid (4.100 g, 19.97 mmol, 90%). mp 58-59 °C; $[\alpha]_D^{21}$ 105 ° (*c* 1.00, $CHCl_3$) (Lit data for opposite enantiomer $[\alpha]_D^{21}$ -103.5° (*c* 0.6, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), 2.55 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ph), 2.71 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ph), 3.56 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 4.87 (1H, br. s, N*H*), 7.02-7.24 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.3 (CH_3), 27.9 (CH_3), 37.5 (CH_2), 63.4 (CH), 83.5 (C), 127.6 (CH), 129.3 (CH), 129.4 (CH), 137.3 (C), 158.3 (C=O). Spectroscopic data essentially identical to literature compound [90]

(*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one, (*S*)-211

Identical method but employing **(*S*)-253**. Yield 89%, $[\alpha]_D^{21}$ -103° (*c* 1.00, $CHCl_3$)

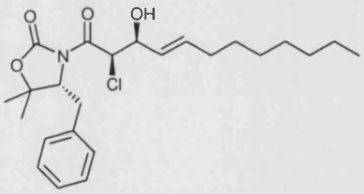
(*R*)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyl-oxazolidin-2-one, 246



N-H oxazolidin-2-one **(*R*)-211** (6.838 g, 30.91 mmol) was dissolved in dry THF and cooled to -78 °C. *n*-BuLi (12.980 mL, 2.5 M, 13.93 mmol) was then added dropwise over 15

minutes and the reaction stirred for a further 15 minutes before the slow addition of chloroacetyl chloride (3.687 mL, 46.56 mmol). The reaction was stirred at -78 °C for a further two hours before quenching with saturated ammonium chloride solution. The mixture was extracted into ether, and the combined organic extracts washed with sodium bicarbonate and brine, dried over MgSO4, filtered and evaporated to dryness to afford the crude product. Recrytallisation (ether / hexane) afforded **(*R*)-4-Benzyl-3-(2-chloroacetyl)-5,5-dimethyl-oxazolidin-2-one 246** as a white crystalline solid (7.663 g, 27.20 mmol, 88%). m.p. 69-70 °C; $[\alpha]_D^{21}$ + 37 ° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (3H, s, C*H*$_3$), 1.33 (3H, s, C*H*$_3$), 2.83 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ph), 3.15 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ph), 4.44 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 4.58 (1H, d (as part of AB quartet), *J* 15.8 Hz, C*H*$_A$H$_B$Cl), 4.70 (1H, d (as part of AB quartet), *J* 15.8 Hz, CH$_A$*H*$_B$Cl), 7.13-7.28 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.8 (CH_3), 29.1 (CH_3), 35.4 (CH_2), 44.3 (CH_2), 64.4 (CH), 84.0 (C), 127.4 (CH), 129.2 (CH), 129.4 (CH), 136.8 (C), 152.7 (C=O), 166.7 (C=O); IR (KBr disc) ν_{max} (cm^{-1}): 1806 (C=O), 1715 (C=O), 791 (C-Cl); MS (CI+, NH_3) *m/z* (%) 299.2 (100) $[M+NH_4]^+$, 265.2 (87), 223.2 (56); HRMS (ES+) for $C_{14}H_{16}ClNO_3$ $[M+H]^+$ Calc. 282.0891, Found 282.0888.

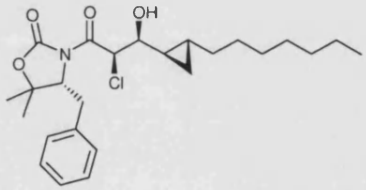
(*R*)-4-Benzyl-3-[(*E*)-(2*R*,3*S*)-2-chloro-3-hydroxy-dodec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 250



According to General Procedure 5, *N*-acyl-oxazolidin-2-one **246** (5.00 g, 17.747 mmol) in DCM at 0 °C was treated with 9-BBNOTf (19.521 mL, 19.521 mmol), ^{i}Pr$_2$NEt (3.709 mL 21.297 mmol) and (*E*)-dec-2-enal (3.910 mL, 21.297 mmol) to afford the crude product in 92% de. Purification *via* column chromatography yielded **(*R*)-4-Benzyl-3-[(*E*)-(2*R*,3*S*)-2-chloro-3-hydroxy-dodec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 250** as a colourless oil (5.725 g, 13.133 mmol, 74%) with >95% de. $[\alpha]_D^{21}$ + 11 ° (*c* 1.0, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (3H, t, *J* 7.0 Hz, *alkyl*-C*H*$_3$), 1.19 (10H, m, *alkyl*-C*H*$_2$), 1.29 (3H, s, C*H*$_3$), 1.34 (3H, s, C*H*$_3$), 1.98 (2H, m, C*H*$_2$CH=CH), 2.62 (1H, br. s, O*H*), 2.85 (1H,

dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.10 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ar), 4.43 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 4.49 (1H, app. t, *J* 5.5 Hz, C*H*OH), 5.44 (1H, ddt, *J* 15.5, 6.5, 1.5 Hz, C(OH)C*H*=C), 5.64 (1H, d, *J* 5.0 Hz, C*H*Cl), 5.74 (1H, dtd, *J* 15.5, 6.5, 1.0 Hz, =C*H*(C$_7$H$_{15}$)), 7.14-7.28 (5H, br. m, *Ar*); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 14.5 (CH$_3$), 22.7 (CH$_3$), 23.1 (CH$_2$), 28.9 (CH$_3$), 29.12 (CH$_2$), 29.4 (CH$_2$), 29.5 (CH$_2$), 32.0 (CH$_2$), 32.6 (CH$_2$), 35.3 (CH$_2$), 59.6 (CH), 64.5 (CH), 73.2 (CH), 83.4 (C), 126.6 (CH), 127.4 (CH), 129.3 (CH), 129.4 (CH), 136.7 (C), 137.1 (CH), 152.3 (C=O), 168.4 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3353 (broad O-H), 1778 (C=O), 1708 (C=O); MS (CI+, NH$_3$) *m/z* (%) 453 (23) [M+NH$_4$]$^+$, 384 (34); HRMS (ES+) for C$_{24}$H$_{34}$ClNO$_4$ [M+NH$_4$]$^+$ Calc. 453.2515, Found 453.2515.

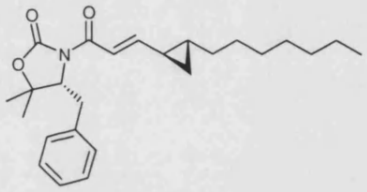
(*R*)-4-Benzyl-3-[(2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-heptylcyclopropyl)-3-hydroxy-propionyl]-5,5-dimethyl-oxazolidin-2-one, 249



α-chloro-β-hydroxy-**250** (4.00g, 9.174 mmol) was dissolved in DCM (in a foil-wrapped flask to keep the contents dark) and cooled to -10 °C. Diethylzinc (45.874 mL, 1.0M in hexane, 45.874 mmol) and diiodomethane (3.700 mL, 45.874 mmol) were added slowly. The reaction was then stirred for a further two hours whilst allowing the reaction to warm slowly to 0 °C. The reaction was quenched by addition of sodium sulphite solution. The resulting white precipitate was redissolved by addition of 2 ml 1.0 N HCl (aq) and the mixture was extracted into DCM. The combined organic extracts were washed with saturated sodium bicarbonate solution and brine, dried with MgSO$_4$, filtered and evaporated to dryness (on a hot water-bath) to yield **(*R*)-4-Benzyl-3-[(2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-heptylcyclopropyl)-3-hydroxy-propionyl]-5,5-dimethyl-oxazolidin-2-one 249** as a pale yellow oil (4.045 g, 8.990 mmol, 98%). $[\alpha]_D^{25}$ + 11.0 (*c* 1.0, CHCl$_3$); ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 0.40 (1H, m, *cyc*-C*H*$_2$), 0.61 (1H, m, *cyc*-C*H*$_2$), 0.79 (1H, m, *cyc*-C*H*), 0.85 (3H, t, *J* 7.0 Hz, C*H*$_3$), 0.90 (1H, m, *cyc*-C*H*), 1.12-1.29 (12H, m, *alkyl*-C*H*$_2$), 1.32 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 2.61 (1H, br. s, O*H*), 2.87 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ph),

3.20 (1H, dd, *J* 14.0, 4.0 Hz, CH_AH_BPh), 3.40 (1H, dd, *J* 8.0, 3.0 Hz, C*H*OH), 4.48 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 5.78 (1H, d, *J* 3.0 Hz, C*H*Cl), 7.17-7.32 (5H, br. m, Ar-*H*); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 10.8 (CH_2), 14.0 (CH_3), 16.6 (CH), 21.7 (CH), 22.3 (CH_3), 22.6 (CH_2), 28.6 (CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 33.4 (CH_2), 34.6 (CH_2), 60.6 (CH), 64.2 (CH), 75.1 (CH), 83.0 (C) 126.9 (CH) 128.7 (CH), 129.0 (CH), 136.4 (C), 151.8 (C=O), 168.3 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3500 (broad O-H), 1770 (C=O), 1716 (C=O); MS (CI+, NH_3) *m/z* (%) 467.3 (44) $[M+NH_4]^+$, 398 (100); HRMS (ES+) for $C_{25}H_{36}ClNO_4$ $[M+NH_4]^+$ Calc. 467.2671, Found 467.2668.

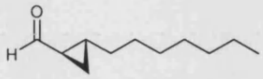
(*R*)-4-benzyl-3-((*E*)-3-((1*R*,2*R*)-2-heptylcyclopropyl)acryloyl)-5,5-dimethyloxazolidin-2-one, 248



Samarium diiodide (11.111 mL, 0.1M in THF, 1.111 mmol) was added dropwise to a solution of **249** (200 mg, 0.444 mmol) stirring in dry THF (5 mL) at room temperature and allowed to stir for a further 30 minutes. The reaction was then quenched with 4 mL 1N HCl (aq) and extracted into ether. The combined organic layers were washed three times with sodium thiosulphate, and then washed with brine, dried with $MgSO_4$, filtered and solvent removed *in vacuo*. The resulting residue was purified *via* column chromatography and **(*R*)-4-benzyl-3-((*E*)-3-((1*R*,2*R*)-2-heptylcyclopropyl)acryloyl)-5,5-dimethyl-oxazolidin-2-one 248** isolated as a pale yellow oil (69 mg, 0.173 mmol, 39%). $[\alpha]_D^{25}$ - 11 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.76–0.88 (5H, m, *cyc*-CH_2, CH_3), 1.05 (1H, m, *cyc*-C*H*), 1.20-1.46 (19H, br. m, 2 x CH_3, *cyc*-C*H*, 6 x *alkyl*-CH_2), 2.85 (1H, dd, *J* 14.0, 4.0 Hz, CH_AH_BPh), 3.19 (1H, dd, *J* 14.0, 9.5 Hz, CH_AH_BPh), 4.52 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 6.63 (1H, dd, *J* 15.0, 10.5 Hz, *H*C=CH), 7.15-7.32 (6H, br. m, HC=C*H*, Ar-*H*); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 16.7 (CH_2), 22.3 (CH), 22.6 (CH_2), 23.1 (CH), 24.1 (CH_3), 28.5 (CH_3), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 33.5 (CH_2), 35.2 (CH_2), 63.7 (CH), 81.9 (C), 116.6 (CH), 126.6 (CH), 128.5 (CH), 129.0 (CH), 137.2 (C), 152.6 (C=O), 156.6 (CH), 165.2 (C); IR (thin film) ν_{max} (cm^{-1}): 1771 (C=O), 1699 (C=O);

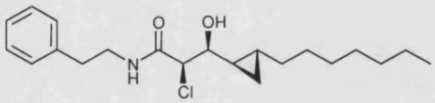
MS (CI+, NH_3) *m/z* (%) 398 (100) $[M+H]^+$, 265 (40); HRMS (ES+) for $C_{25}H_{35}NO_3$ $[M+H]^+$ Calc. 398.2690, Found 398.2690.

(1*R*,2*R*)-2-heptylcyclopropanecarbaldehyde, 257



In the attempted synthesis of **248** from **249**, **(1*R*,2*R*)-2-heptylcyclopropanecarbaldehyde 257** was also formed and was recovered after column chromatography (13.5 mg, 0.080 mmol, 18%) as a colourless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.85 – 0.99 (4H, m, including 3H, t, *J* 7.2 Hz at 0.89, C*H*$_3$, *cyc*-C*H*$_A$H$_B$); 1.25 – 1.55 (14H, m, 6 x alkyl-C*H*$_2$, *cyc*-CH$_A$*H*$_B$ and *cyc*-C*H*), 1.61 (1H, m, *cyc*-C*H*), 9.08 (1H, d, *J* 5.5 Hz, C*H*O); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 15.0 (CH_3), 16.3 (CH_2), 23.8 (CH), 24.1 (CH), 30.6 (CH_2), 30.7 (CH_2), 31.6 (CH_2), 32.4 (CH_2), 33.5 (CH_2), 34.1 (CH_2), 202.8 (C=O). Spectroscopic data essentially identical to literature precedent. [97]

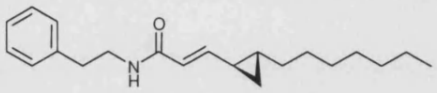
2*R*,3*S*)-2-chloro-3-((1'*R*,2'*R*)-2-heptyl-cyclopropyl)-3-hydroxy-*N*-phenethyl-propionamide, 263



Oxazolidin-2-one **249** (1.00g, 2.22 mmol) was dissolved in neat phenylethylamine (8 mL) and stirred for 16 hours at room temperature. After this time, the whole reaction mixture was applied to a large pad of silica to ensure retention of the excess amine. **2*R*,3*S*)-2-chloro-3-((1'*R*,2'*R*)-2-heptyl-cyclopropyl)-3-hydroxy-*N*-phenethyl-propionamide 263** was isolated as an off-white solid (724 mg, 1.98 mmol, 89%). m.p. 64-65 °C; $[\alpha]_D^{25}$ – 23 (*c* 1.0 ,$CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.39 (1H, m, *cyc*-C*H*$_A$H$_B$), 0.59 (1H, m, *cyc*-CH$_A$*H*$_B$), 0.70 (1H, m, *cyc*-C*H*), 0.87 (3H, t, *J* 7.0 Hz, C*H*$_3$), 0.88 (1H, m, *cyc*-C*H*), 1.13-1.34 (12H, m, C*H*$_2$), 2.83 (2H, t, *J* 7.0 Hz, C*H*$_2$Ph), 3.49 (2H, m, NC*H*$_2$), 3.55 (1H, m, C*H*OH), 4.43 (1H, d, *J* 3.0 Hz, C*H*Cl), 6.77 (1H, br. s, N*H*), 7.18-7.34 (5H, br. m, Ar-*H*); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 11.3 (CH_2), 14.6 (CH_3), 17.2 (CH), 22.3 (CH), 23.0 (CH_2), 29.7 (CH_2), 29.8 (2 x CH_2), 32.2 (CH_2), 33.8 (CH_2), 35.8 (CH_2), 41.5 (CH_2), 64.9 (CH),

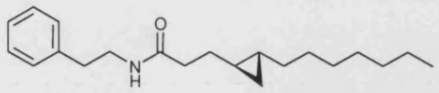
76.3 (CH), 127.0 (CH), 129.0 (CH), 129.2 (CH), 138.8 (C), 168.3 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3477 (broad O-H), 1647 (C=O); MS (CI+, NH_3) *m/z* (%) 366 (45) $[M+H]^+$, 314 (100); HRMS (ES^+) for $C_{21}H_{33}ClNO_2$ $[M+H]^+$ Calc. 366.2194, Found 366.2198.

(*E*)-3-((1*R*,2*R*)-2-Heptyl-cyclopropyl)-*N*-phenethyl-acrylamide, 264



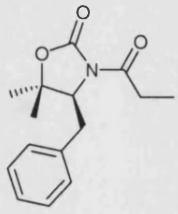
Samarium diiodide (41.0 mL, 0.1 M in THF, 4.10 mmol) was added slowly to a solution of **263** (600 mg, 1.64 mmol) stirring in dry THF (10 mL) at room temperature and allowed to stir for a further 30 minutes. The reaction was then quenched with 15 mL 1N HCl (aq) and extracted into ether. The combined organic layers were washed three times with sodium thiosulphate, and then washed with brine, dried with $MgSO_4$, filtered and solvent removed *in vacuo*. The resulting residue was purified *via* column chromatography affording **(*E*)-3-((1*R*,2*R*)-2-Heptyl-cyclopropyl)-*N*-phenethyl-acrylamide 264** as a white solid (437 mg, 1.39 mmol, 85%). m.p. 65-66 °C; $[\alpha]_D^{25}$ -37 (*c* 0.99, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.67 (1H, m, *cyc*-C*H*$_A$H$_B$), 0.75 (1H, m, *cyc*-CH$_A$*H*$_B$), 0.87 (3H, t, *J* 7.0 Hz, C*H*$_3$), 0.94 (1H, m, *cyc*-C*H*), 1.17-1.40 (13H, br. m, C*H*$_2$ and *cyc*-C*H*), 2.83 (2H, app. t, *J* 7.0 Hz, PhC*H*$_2$), 3.57 (2H, q, *J* 7.0 Hz, C*H*$_2$NH), 5.43 (1H, br. s, N*H*), 5.71 (1H, d, *J* 15.0 Hz, C=*H*), 6.35 (1H, dd, *J* 15.0, 10.2 Hz, C=*H*), 7.16-7.34 (5H, br. m, Ar-*H*); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.5 (CH_3), 15.9 (CH_2), 22.2 (CH), 23.0 (CH_2), 23.2 (CH), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 32.2 (CH_2), 34.0 (CH_2), 36.1 (CH_2), 40.9 (CH_2), 120.0 (CH), 126.8 (CH), 129.0 (CH), 129.2 (CH), 139.4 (C), 149.9 (CH), 166.5 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3398 (broad O-H), 1663 (C=O); MS (CI+, NH_3) *m/z* (%) 314 (100) $[M+H]^+$; HRMS (ES^+) for $C_{21}H_{31}NO$ $[M+H]^+$ Calc. 314.2477, Found 314.2478.

3-((1'*R*,2'*R*)-2'-heptyl-cyclopropan-1-yl)-*N*-phen-ethyl-propionamide (Grenadamide) 240



A solution of **264** (250 mg, 0.798 mmol) in MeOH / THF (2:1) (9 mL) was added to a flask charged with $CoCl_2.6H_2O$ (37.9 mg, 0.160 mmol) and the mixture stirred for 30 minutes. A solution of $NaBH_4$ (120 mg, 3.192 mmol) in DMF (3 mL) was then added and the reaction stirred for a further 3 hours. After this time, the reaction mixture was diluted with 5 mL water and extracted into DCM. The combined organic fractions were washed three times with water, washed with brine, dried with $MgSO_4$, filtered and solvent removed *in vacuo* to afford the crude product. Column chromatography afforded **3-((1'*R*,2'*R*)-2'-heptyl-cyclopropan-1-yl)-*N*-phenethyl-propionamide (Grenadamide) 240** as a white solid (221 mg, 0.702 mmol, 88%). m.p. 46-47 °C; $[\alpha]_D^{25}$ - 11.0 (*c* 1.0, $CHCl_3$) (Lit. $[\alpha]_D^{25}$ - 11.0, *c* 0.1, $CHCl_3$);[96] ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.16 (2H, m, *cyc*-C*H*$_2$), 0.38 (2H, m, 2 × *cyc*-C*H*), 0.87 (3H, t, *J* 7.0 Hz, C*H*$_3$), 1.14 (2H, m, C*H*$_2$), 1.24-1.33 (10H, m, C*H*$_2$), 1.49 (2H, m, C*H*$_2$), 2.18 (2H, t, *J* 7.5 Hz, C*H*$_2$CO), 2.81 (2H, t, *J* 7.0 Hz, PhC*H*$_2$), 3.52 (2H, q, *J* 6.8 Hz, C*H*$_2$NH), 5.51 (1H, br. s, N*H*), 7.17-7.34 (5H, br. m, Ar*H*); ^{13}C-NMR ($CDCl_3$, 75 MHz): 12.2 (CH_2), 14.5 (CH_3), 18.6 (CH), 19.3 (CH), 23.1 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 30.7 (CH_2), 32.3 (CH_2), 34.5 (CH_2), 36.1 (CH_2), 37.3 (CH_2), 40.9 (CH_2), 126.9 (CH), 129.0 (CH), 129.2 (CH), 139.3 (C), 173.5 (C=O); IR (KBr) ν_{max} (cm^{-1}): 1638 (C=O); MS (CI+, NH_3) *m/z* (%) 316 (100) $[M+H]^+$; HRMS (ES^+) for $C_{21}H_{34}NO$ $[M+H]^+$ Calc. 316.2635, Found 316.2637.

(*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one, 230



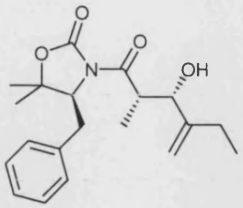
According to general procedure 2, (*S*)-4-benzyl-oxazolidin-2-one **(*S*)-211** (3.675 g, 16.610 mmol) treated with *n*-butyl lithium (6.976 mL, 2.5 M, 17.441 mmol) and propionyl

chloride (2.175 mL, 24.915 mmol) to afford (*S*)-**230** (3.602g, 13.786 mmol, 83%) as white needles. m. p. 61-62 °C; $[\alpha]_D^{21}$ -41° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.07 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.29 (3H, s, CH_3), 1.30 (3H, s, CH_3), 2.81 (1H, dd, *J* 14.0, 9.5 Hz, CH_AH_BAr), 2.86 (2H, q, *J* 7.0 Hz, CH_2CH_3), 3.08 (1H, dd, *J* 14.0, 4.0 Hz, CH_AH_BAr), 4.44 (1H, dd, *J* 9.5, 4.0 Hz, CHN), 7.12 (5H, br. m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 8.7 (CH_3), 22.7 (CH_3), 28.9 (CH_3), 29.7 (CH_2), 35.7 (CH_2), 63.9 (CH), 82.6 (C), 127.2 (CH), 129.1 (CH), 129.4 (CH), 137.4 (C), 153.1 (C=O), 174.7 (C=O); IR (KBr disc) ν_{max} (cm^{-1}): 1771 (C=O), 1707 (C=O); MS (CI+, NH_3) *m/z* (%) 262 (48) $[M+H]^+$, 279 (100) $[M+NH_3]^+$; HRMS (ES+) for $C_{15}H_{19}NO_3$ $[M+H]^+$ Calc. 262.1438, Found 262.1442.

General procedure 16: Solid phase *syn*-aldol reaction

Functionalised resin (1 equiv.) sealed into an IRORI minikan and placed into an oven-dried round bottomed flask. DCM (8 mL) was added to preswell the resin and the flask cooled to 0 °C. 9-BBN-OTf (0.5 M in DCM, 5.0 equiv.) was added slowly and the reaction stirred for one hour before removal of the reaction solution *via* cannula. Fresh, pre-chilled DCM (10 mL was then added to resuspend the resin and $^iPr_2NEt$ (5.0 equiv.) added and the reaction stirred for a further hour. Finally the entire reaction was cooled to -78 °C before the addition of aldehyde (7.0 equiv.), with the reaction then being allowed to warm slowly to room temperature whilst stirring for a further 12 hours. In order to quench the reaction, phosphate buffer pH 7 (0.1 M) was added and the resin immediately filtered and washed thoroughly (DCM, DCM/MeOH, THF) in alternate cycles. Side chain cleavage of the resulting aldol-functionalised resin was achieved according to General procedure 9 (LiOOH) or 11 ($NaBH_4$).

(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-hexanoyl)-5,5-dimethyl-oxazolidin-2-one, 270



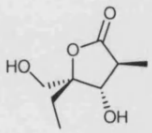
According to general procedure 5, employing *N*-propionyl-oxazolidin-2-one **(*S*)-230** (1.000g, 3.827 mmol) in DCM (40 mL), 9-BBN-OTf (8.419 mL, 0.5 M, 4.209 mmol), $^{i}Pr_2NEt$ (0.800 mL, 4.592 mmol) and 2-ethylacrolein (0.440 mL, 4.592 mmol), the crude product was prepared as a pale yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-hexanoyl)-5,5-dimethyl-oxazolidin-2-one 270** (1.070 g, 3.10 mmol, 81%) as a colourless oil. $[\alpha]_D^{21}$ - 36 ° (*c* 1.0, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1. 07 (3H, t, *J* 7.0, CH_2CH_3), 1.11 (3H, d, *J* 7.0, CH_3), 1.38 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.02 (2H, m, CH_2CH_3), 2.78 (1H, br. s, O*H*), 2.91 (1H, dd, *J* 14.0, 9.5 Hz, CH_AH_BAr), 3.08 (1H, dd, *J* 14.0, 4.0 Hz, CH_AH_BAr), 3.96 (1H, dq, *J* 3.5, 7.0 Hz, $CHCH_3$), 4.40 (1H, d, *J* 3.5 Hz, C*H*OH), 4.53 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 4.98 (1H, app. t, *J* 1.0 Hz, $C=CH_AH_B$), 5.16 (1H, app. t, *J* 1.0 Hz, $C=CH_AH_B$), 7.20-7.34 (5H, br. m, Ar*H*) ; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.0 (CH_3), 12.5 (CH_3), 22.6 (CH_3), 25.7 (CH_2), 28.8 (CH_3), 35.8 (CH_2), 41.0 (CH), 63.8 (CH), 74.0 (CH), 82.7 (C), 109.9 (CH_2), 127.3 (CH), 129.1 (CH), 129.5 (CH), 137.0 (C), 150.2 (C), 152.6 (C=O), 177.6 (C=O) ; IR (thin film) ν_{max} (cm^{-1}): 3497 (broad O-H), 1773 (C=O), 1700 (C=O); MS (CI+, NH_3) *m/z* (%) 346 (38) $[M+H]^+$, 279 (100), 262 (83), 223 (45) ; HRMS (ES+) for $C_{20}H_{27}NO_4$ $[M+H]^+$ Calc. 346.2013, Found 346.2014.

General procedure 17: Solution phase epoxidation / lactonisation

Solution of aldol substrate (1.0 equiv) in benzene added to $VO(acac)_2$ (0.2 equiv) and stirred for 5 minutes. *t*-BuOOH (1.1 equiv.) added dropwise and reaction stirred at room temperature for a further 3 hours. After this time, reaction quenched by addition of saturated ammonium chloride solution and extracted into ether, with these organic fractions being retained in the case of non-water soluble lactones. The aqueous layer was then

saturated with sodium chloride and back extracted into fresh EtOAc. The new organic fractions were combined, dried with MgSO4, filtered and solvent removed *in vacuo* to yield the crude lactone product.

(3*S*,4*S*,5*S*)-5-ethyl-dihydro-4-hydroxy-5-(hydroxymethyl)-3-methylfuran-2(3H)-one, 274

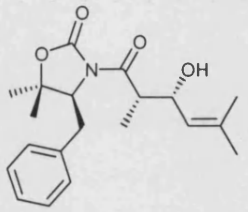


Solution phase method: According to General Procedure 16, employing aldol **270** (200.00 mg, 0.579 mmol) in benzene (8.0 mL), $VO(acac)_2$ (31.0 mg, 0.116 mmol) and *t*-BuOOH (0.12 mL, 5.5 M, 0.637 mmol) the crude lactone was prepared. Recrystallisation (ether) afforded **(3*S*,4*S*,5*S*)-5-ethyl-dihydro-4-hydroxy-5-(hydroxymethyl)-3-methylfuran-2(3H)-one 274** (78 mg, 0.452 mmol, 78%) as a white solid. m.p. 76-77 °C; $[\alpha]_D^{21}$ - 19 ° (*c* 0.16, CH_2Cl_2); ^{1}H NMR (D_2O, 300 MHz): δ 0.72 (3H, t, *J* 7.5 Hz, C*H*$_3$CH$_2$), 1.03 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 1.47 – 1.59 (2H, app. qd, *J* 7.5, 2.5 Hz, C*H*$_2$CH$_3$), 2.77 (1H, dq, *J* 9.5, 7.0 Hz, C*H*CH$_3$), 3.52 (1H, d, *J* 13.0 Hz, C*H*$_A$H$_B$OH), 3.71 (1H, d, *J* 13.0 Hz, CH$_A$*H*$_B$OH), 3.91 (1H, d, *J* 9.5 Hz, C*H*OH); ^{13}C NMR (D_2O, 75.5 MHz): δ 6.9 (CH_3), 12.8 (CH_3), 27.4 (CH_2), 43.3 (CH), 62.5 (CH_2), 77.9 (CH), 89.7 (C), 181.0 (C=O); IR (KBr disc) ν_{max} (cm^{-1}): 3348 (broad OH), 1751 (C=O); HRMS (ES+) for $C_8H_{14}O_4$ $[M+H]^+$ Calc 192.1230, Found 192.1233.

Solid phase method: Aldol-functionalised resin **295** (200mg, 0.90mmol/g, 0.18 mmol), preswollen in benzene (8 mL) was treated with $VO(acac)_2$ (23.8 mg, 0.09 mmol) , and agitated for 30 minutes, followed by *t*-BuOOH (0.098 mL, 5.5 M, 0.54 mmol). The reaction was then agitated on an orbital shaker for 16 hours at room temperature. The resin was then filtered and washed thoroughly (DCM, DCM / MeOH) with all washings collected and evaporated to dryness. The resulting green residue was redissolved in DCM and passed through a plug to silica to afford **(3*S*,4*S*,5*S*)-5-ethyl-dihydro-4-hydroxy-5-(hydroxymethyl)-3-methylfuran-2(3H)-one 274** (16.9 mg, 0.097 mmol, 58%) as a

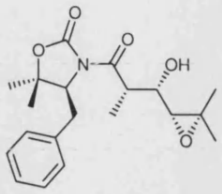
colourless oil, which later solidified. Spectroscopic data identical to that reported above. For X-ray structure, see Appendix.

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2,5-dimethyl-hex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 277



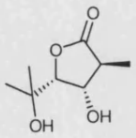
According to General Procedure 5 using *N*-acyl SuperQuat oxazolidinone **(*S*)-230** (1.500 g, 5.740 mmol), 9-BBN-OTf (12.63 mL, 0.5 M, 6.314 mmol), DIPEA (1.199 mL, 6.888 mmol) and 3-methylcrotonaldehyde (0.605 mL, 6.314 mmol) with the reaction stirred at rt for 18 h, the crude product was prepared as a pale yellow oil . Column chromatography on silica using 4:1 petroleum ether (b.p.40-60 °C)/ethyl acetate as the eluent yielded **277** as a colourless oil (1.784 g, 5.166 mmol, 90%). $[\alpha]_D^{21}$ - 27° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.11 (3H, d, *J* 7.0 Hz, $CHCH_3$), 1.30 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.61 (3H, d, *J* 1.5 Hz, $C=C(CH_3)(CH_3)$), 1.65 (3H, d, *J* 1.0, $C=C(CH_3)(CH_3)$), 2.83 (1H, dd, *J* 14.0, 9.5 Hz, CH_AH_BAr), 2.98 (1H, dd, *J* 14.0, 4.0 , CH_AH_BAr), 3.86 (1H, dq, *J* 5.0, 7.0 Hz, $CHCH_3$), 4.45 (1H, dd, *J* 9.5, 4.0 Hz, CHN), 4.53 (1H, dd, *J* 8.5, 5.0 Hz, CHOH), 5.17 (1H, dm, *J* 8.5Hz, HC=C), 7.13-7.27 (5H, br. m, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 12.6 (CH_3), 18.8 (CH_3), 22.5 (CH_3), 26.4 (CH_3), 28.6 (CH_3), 35.9 (CH_2), 43.4 (CH), 63.8 (CH), 69.9 (CH), 82.6 (C), 124.5 (CH), 127.3 (CH), 129.0 (CH), 129.5 (CH), 137.1 (C), 137.2 (C), 153.0 (C=O), 176.7 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3479 (broad O-H), 1769 (C=O), 1681 (C=O); MS (CI+, NH_3) *m/z* (%) 363 (19) $[M+NH_4]^+$, 346 (20) $[M+H]^+$, 328 (100) [M-H2O]+, 279 (75), 223 (42), 102 (97); HRMS (ES+) for $C_{20}H_{27}NO_4$ $[M+H]^+$ Calc. 346.2013, Found 346.2011.

4-Benzyl-3-[(2S,3S)-3-((2R,3R)-3-ethyl-3-methyl-oxiranyl)-3-hydroxy-2-methyl-propionyl]-5,5-dimethyl-oxazolidin-2-one, 284



According to General Procedure 17, employing aldol **277** (200 mg, 0.579 mmol) in benzene (8.0 mL), $VO(acac)_2$ (31.0 mg, 0.116 mmol) and *t*-BuOOH (0.12 mL, 5.5 M, 0.637 mmol), crude **284** was prepared. Purification *via* recrystallisation (Et_2O, Hexane) gave **284** (153 mg, 0.442 mmol, 73% yield, >95% de). mp decomposed >50 °C; $[\alpha]_D^{25}$ -10 (c 0.48, CH_2Cl_2); ^1H NMR (Benzene-d^6, 300 MHz): δ 0.85 (3H, s, epoxide-C*H*$_3$), 0.86 (3H, s, epoxide-C*H*$_3$), 1.03 (3H, s, C*H*$_3$), 1.17 (3H, s, C*H*$_3$), 1.25 (1H, d, *J* 7.0 Hz, C*H*$_3$CH), 2.36 (1H, obs. d, *J* 4.0 Hz, OH), 2.37 (1H, obs. dd, *J* 14.5, 9.5 Hz, CH_AH_BPh), 2.88 (1H, dd, *J* 14.5, 4.0 Hz, CH_AH_BPh), 3.00 (1H, d, *J* 7.0 Hz, epoxide-C*H*), 3.80 (1H, m, C*H*CH_3), 4.33 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 4.41 (1H, dd, *J* 7.0, 5.5 Hz, C*H*OH), 7.23-6.96 (5H, m, Ph); ^{13}C NMR (Benzene-d^6, 75.5 MHz): δ 12.9 (CH_3), 19.9 (CH_3), 22.2 (CH_3), 25.2 (CH_3), 28.2 (CH_3), 35.7 (CH_2), 42.1 (CH), 59.6 (CH), 64.1 (CH), 65.5 (C), 71.4 (CH), 82.1 (C), 127.3 (CH), 129.2 (CH), 129.8 (CH), 137.9 (C), 152.9 (C=O), 175.3 (C=O): IR (KBr / cm^{-1}) 3466 (broad O-H), 1776 (C=O), 1693 (C=O); HRMS: no molecular ion found.

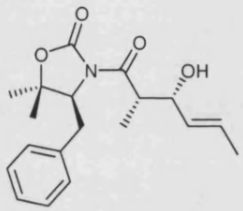
(3*S*,4*S*,5*R*)-dihydro-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methylfuran-2(3H)-one, 278



According to General Procedure 17, employing aldol **277** (200 mg, 0.579 mmol) in benzene (8.0 mL), $VO(acac)_2$ (31.0 mg, 0.116 mmol) and *t*-BuOOH (0.12 mL, 5.5 M, 0.637 mmol) but stirring for 12 hours, the crude lactone was prepared. Recrystallisation (ether) afforded **(3*S*,4*S*,5*R*)-dihydro-4-hydroxy-5-(2-hydroxypropan-2-yl)-3-methylfuran-2(3H)-one 278** (76 mg, 0.434 mmol, 75%) as a pale yellow solid. m.p. 71 – 72 °C; $[\alpha]_D^{21}$ 16 ° (*c*

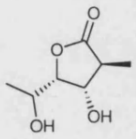
0.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.33 (6H, s, 2 x C*H*$_3$), 2.68 (1H, m, C*H*CH$_3$), 3.96 (1H, d, *J* 7.0 Hz, C*H*C(CH$_3$)$_2$OH), 4.18 (1H, app. t, *J* 7.0 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.4 (CH_3), 24.7 (CH_3), 25.0 (CH_3), 42.8 (CH), 69.6 (C), 73.4 (CH), 86.7 (CH), 175.16 (C=O); IR (KBr disc) ν_{max} (cm^{-1}): 3356 (broad OH), 1758 (C=O); MS (CI+, NH_3) *m/z* (%) 192 (100) $[M+NH_4]^+$, 115 (27), 52 (56); HRMS (ES+) for $C_8H_{14}O_4$ $[M+NH_4]^+$ Calc. 192.1230, Found 192.1231.

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-hex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 279



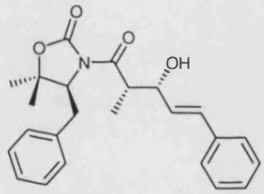
According to General Procedure 5 using *N*-acyl SuperQuat oxazolidinone **(*S*)-230** (1.00 g, 3.827 mmol), 9-BBN-OTf (8.419 mL, 0.5 M, 4.209 mmol), DIPEA (0.799 mL, 4.593 mmol) and crotonaldehyde (0.349 mL, 4.209 mmol) with the reaction stirred at rt for 18 h, the crude product was prepared as a dark yellow oil. Column chromatography on silica using 4:1 petroleum ether (b.p.40-60 °C)/ethyl acetate as the eluent yielded **279** as a colourless oil (1.1726 g, 3.538 mmol, 93%). $[\alpha]_D^{21}$ -22 ° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.06 (3H, d, *J* 7.0 Hz, CHC*H*$_3$), 1.29 (3H, s, C*H*$_3$), 1.30 (3H, s, C*H*$_3$), 1.61 (3H, ddd, *J* 6.5, 1.5, 1.0 Hz, C=CHC*H*$_3$), 2.49 (1H, br. s, O*H*), 2.82 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.97 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ar), 3.82 (1H, dq, *J* 4.5, 7.0 Hz, C*H*CH$_3$), 4.26 (1H, m, C*H*OH), 4.44 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 5.39 (1H, ddq, *J* 15.5, 6.5, 1.5 Hz, *H*C=CHCH$_3$), 5.65 (1H, dqd, *J* 15.5, 6.5, 1.0 Hz, HC=C*H*CH$_3$), 7.11-7.25 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 12.2 (CH_3), 18.2 (CH_3), 22.5 (CH_3), 28.7 (CH_2), 35.9 (CH_2), 43.2 (CH), 63.8 (CH), 73.6 (CH), 82.7 (C), 127.3 (CH), 128.9 (CH), 128.1 (CH), 129.5 (CH), 130.6 (CH), 137.1 (C), 152.9 (C=O), 176.9 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3497 (broad O-H), 1777 (C=O), 1697 (C=O); MS (CI+, NH_3) *m/z* (%) 332 (60) $[M+H]^+$, 349 (100) $[M+NH_4]^+$; HRMS (ES+) for $C_{19}H_{25}NO_4$ $[M+H]^+$ Calc. 332.1856, Found 332.1858.

(3S,4S,5S)-4-Hydroxy-5-(1-hydroxy-ethyl)-3-methyl-dihydro-furan-2-one, 280



According to General Procedure 17, employing aldol **279** (200 mg, 0.61 mmol) in benzene (8 mL), $VO(acac)_2$ (33.0 mg, 0.122 mmol) and *t*-BuOOH (0.12 mL, 5.5 M, 0.67 mmol), the crude lactone was prepared. Column chromatography afforded **280** (37.1 mg, 0.24 mmol, 38% yield, >95% de) as a colourless oil. ^{1}H NMR (d_4-MeOD, 300 MHz): δ 1.15 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.53 (3H, d, *J* 7.0 Hz, C*H*$_3$CHOH), 2.63 (1H, m, C*H*CH$_3$), 3.92 (2H, m, C*H*OH, C*H*O), 4.14 (1H, m, (CH$_3$)C*H*OH); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 14.3 (CH$_3$), 22.4 (CH$_3$), 44.7 (CH), 65.7 (CH), 82.7 (CH), 87.5 (CH), 180.0 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3351 (broad O-H), 1754 (C=O).

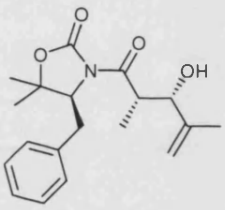
(*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-3-hydroxy-2-methyl-5-phenyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 281



According to General Procedure 5 using *N*-acyl SuperQuat oxazolidinone **(*S*)-230** (1.000 g, 3.827 mmol), 9-BBN-OTf (8.419 mL, 0.5 M, 4.209 mmol), DIPEA (0.799 mL, 4.593 mmol) and *trans*-cinnamaldehyde (0.531 mL, 4.209 mmol) with the reaction stirred at room temperature for 18 h, the crude product was prepared as a pale yellow solid . Recrystallisation (petroleum ether (b.p.40-60 °C)/ethyl acetate) yielded **281** as a colourless crystalline solid (1.325 g, 3.367 mmol, 88%). m.p. 148-149 °C ; $[\alpha]_D^{21}$ 4 ° (*c* 1.1, CH_2Cl_2) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.13 (3H, d, *J* 7.0 Hz, CHC*H*$_3$), 1.25 (3H, s, C*H*$_3$), 1.33 (3H, s, C*H*$_3$), 2.78 (1H, d, *J* 2.0 Hz, O*H*), 2.85 (1H, dd, *J* 14.0, 9.5 Hz, C*H*$_A$H$_B$Ar), 3.00 (1H, dd, *J* 14.0, 4.0 Hz, CH$_A$*H*$_B$Ar), 3.93 (1H, dq, *J* 4.0, 7.0 Hz, C*H*CH$_3$), 4.48 (1H, dd, *J* 9.5, 4.0 Hz, C*H*N), 4.55 (1H, m, C*H*OH), 6.12 (1H, dd, *J* 16.0, 6.0 Hz,

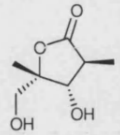
*H*C=CHAr), 6.59 (1H, dd, *J* 16.0, 1.5 Hz, HC=C*H*Ar), 7.13-7.33 (10H, br. m, Ar*H*) ; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 12.1 (CH_3), 22.6 (CH_3), 28.7 (CH_3), 35.9 (CH_2), 43.3 (CH), 63.7 (CH), 73.3 (CH), 82.8 (C), 126.9 (CH), 127.3 (CH), 128.1 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.5 (CH), 131.9 (CH), 135.2 (C), 136.9 (C), 152.8 (C=O), 177.0 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3510 (broad O-H), 1771 (C=O), 1674 (C=O); MS (CI+, NH_3) *m/z* (%) 393 (80), 395 (57), 411 (100) $[M+NH_4]^+$; HRMS (ES+) for $C_{24}H_{27}NO_4$ $[M+H]^+$ Calc. 411.2278, Found 411.2273.

(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,4-dimethyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 282



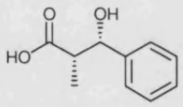
According to general procedure 5, employing *N*-propionyl-oxazolidin-2-one **(*S*)-230** (1.300g, 4.974 mmol) in DCM (60 mL), 9-BBN-OTf (10.94 mL, 0.5 M, 5.471 mmol), $^{i}Pr_2NEt$ (1.040 mL, 5.969 mmol) and methacrolein (0.492 mL, 5.969 mmol), the crude product was prepared as a yellow oil. Purification *via* column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,4-dimethyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 282** (1.467 g, 4.427 mmol, 89%) as a colourless oil. $[\alpha]_D^{21}$ - 33 ° (*c* 1.05, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04 (3H, d, *J* 7.2, CHC*H*$_3$), 1.29 (3H, s, C*H*$_3$), 1.31 (3H, s, C*H*$_3$), 1.65 (3H, s, C(=C)C*H*$_3$), 2.83 (1H, dd, *J* 14.0, 9.5, C*H*$_A$H$_B$Ar), 2.99 (1H, dd, *J* 14.0, 4.0, CH$_A$*H*$_B$Ar), 3.91 (1H, dq, *J* 4.0, 7.0, C*H*CH$_3$), 4.28 (1H, d, *J* 4.0, C*H*OH), 4.45 (1H, dd, *J* 9.5, 4.0, C*H*N), 4.86 (1H, br. s, C=C*H*$_A$H$_B$), 5.00 (1H, br. s, C=CH$_A$*H*$_B$), 7.11-7.25 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.1 (CH_3), 19.6 (CH_3), 22.6 (CH_3), 28.8 (CH_3), 35.7 (CH_2), 40.8 (CH), 63.8 (CH), 74.7 (CH), 82.8 (C), 112.3 (CH_2), 127.3 (CH), 129.1 (CH), 129.6 (CH), 137.1 (C), 144.4 (C), 152.7 (C=O), 177.3 (C=O) ; IR (thin film) ν_{max} (cm^{-1}): 3516 (broad O-H), 1777 (C=O), 1693 (C=O); MS (CI+, NH_3) *m/z* (%) 332 (40) $[M+H]^+$, 279 (100), 262 (83), 223 (89); HRMS (ES+) for $C_{19}H_{25}NO_4$ $[M+H]^+$ Calc. 332.1856, Found 332.1856.

(3*S*,4*S*,5*S*)-dihydro-4-hydroxy-5-(hydroxymethyl)-3,5-dimethylfuran-2(3H)-one, 283



According to General Procedure 17, employing aldol **282** (200.00 mg, 0.603 mmol) in benzene (8.0 mL), $VO(acac)_2$ (32.0 mg, 0.121 mmol) and *t*-BuOOH (0.12 mL, 5.5 M, 0.663 mmol) the crude lactone was prepared. Recrystallisation (ether) afforded **(3*S*,4*S*,5*S*)-dihydro-4-hydroxy-5-(hydroxymethyl)-3,5-dimethylfuran-2(3H)-one 283** (67.6 mg, 0.422 mmol, 70%) as a white crystalline solid (plates). m.p. 105-106 °C; $[\alpha]_D^{21}$ -27.2 ° (*c* 0.85, $CHCl_3$); ^{1}H NMR (D_2O, 300 MHz): 1.29 (3H, d, *J* 7.3 Hz, $CHCH_3$), 1.42 (3H, s, CCH_3), 3.04 (1H, dq, *J* 9.5, 7.0 Hz, $CHCH_3$), 3.71 (1H, d, *J* 13.0 Hz, CH_AH_BOH), 3.94 (1H, d, *J* 13.0 Hz, CH_AH_BOH), 4.11 (1H, d, *J* 9.5 Hz, CHOH); ^{13}C NMR (D_2O, 75.5 MHz): δ 12.5 (CH_3), 20.7 (CH_3), 42.7 (CH), 63.5 (CH_2), 80.0 (CH), 87.3 (C), 180.5 (C=O); IR (KBr disc) ν_{max} (cm^{-1}): 3340 (broad OH), 2956, 1750 (C=O), 1440, 1320, 1170; MS (CI+, NH_3) *m/z* (%) 178 (88) $[M+NH_4]^+$, 160 (19) $[M+H]^+$, 130 (100); HRMS (ES+) for $C_7H_{12}O_4$ $[M+NH_4]^+$ Calc. 178.1074, Found 178.1074.

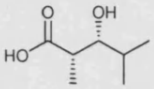
(2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropanoic acid, 288



According to General Procedure **16** employing *N*-propionyl-oxazolidin-2-one resin **73a** (200 mg, 0.95 mmol/g, 0.19 mmol), 9-BBNOTf (1.90 mL, 0.5 M, 0.95 mmol), ^{i}Pr$_2$NEt (0.165 ml, 0.95 mmol) and benzaldehyde (0.135 mL, 1.33 mmol), aldol-functionalised resin **291** was prepared (not shown). LiOOH cleavage, according to General Procedure 9, employing the aldol-functionalised resin (0.19 mmol) preswollen in THF (4 mL), H_2O_2 (0.18 mL, 1.90 mmol) and LiOH (39.9 mg, 0.95 mmol) dissolved in 0.5 mL H_2O, afforded **(2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropanoic acid 288** as a colourless oil (19.9 mg, 0.11 mmol, 58%). $[\alpha]_D^{21}$ -29.0 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.12 (3H,

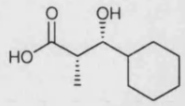
d, *J* 7.0 Hz, CH_3), 2.81 (1H, dq, *J* 4.0, 7.0 Hz, C*H*CH_3), 5.16 (1H, d, *J* 4.0 Hz, C*H*OH), 7.24-7.36 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 10.2 (CH_3), 46.2 (CH), 73.5 (CH), 125.9 (CH), 127.8 (CH), 129.3 (CH), 140.9 (C), 180.6 (C=O). Spectroscopic data identical to literature compound.[58]

(2*S*,3*R*)-3-hydroxy-2,4-dimethylpentanoic acid, 289



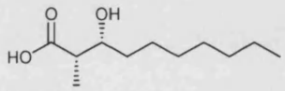
Accordng to General Procedure 16, employing *N*-propionyl-oxazolidin-2-one resin **73a** (200 mg, 0.95 mmol/g, 0.19 mmol), 9-BBNOTf (1.90 mL, 0.5 M, 0.95 mmol), $^{i}Pr_2NEt$ (0.165 ml, 0.95 mmol) and isobutyraldehyde (0.121 mL, 1.33 mmol), aldol-functionalised resin was prepared (not shown). LiOOH cleavage, according to General Procedure 9, employing the aldol-functionalised resin preswollen in THF (4 mL), H_2O_2 (0.18 mL, 1.90 mmol) and LiOH (39.9 mg, 0.95 mmol) dissolved in 0.5 mL H_2O, afforded **(2*S*,3*R*)-3-hydroxy-2,4-dimethylpentanoic acid 289** as a colourless oil (17.5 mg, 0.120 mmol, 63%). $[\alpha]_D^{21}$ -9.5 ° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85 (3H, d, *J* 7.0 Hz, CH_3), 0.98 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.17 (3H, d, *J* 7.0 Hz, CHC*H*$_3$), 1.67 (1H, m, C*H*$(CH_3)_2$), 2.65 (1H, dq, *J* 3.5, 7.0 Hz, COC*H*CH_3), 3.59 (1H, dd, *J* 7.5, 3.5 Hz, C*H*OH), 4.65 (1H, br. s, O*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.3 (CH_3), 17.1 (CH_3), 19.6 (CH_3), 30.9 (CH), 40.9 (CH), 77.6 (CH), 180.4 (C=O). Spectroscopic data identical to literature compound.[58]

(2*S*,3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropanoic acid, 290



According to General Procedure 16, employing *N*-propionyl-oxazolidin-2-one resin **73a** (200 mg, 0.95 mmol/g, 0.19 mmol), 9-BBNOTf (1.90 mL, 0.5 M, 0.95 mmol), $^{i}Pr_2NEt$ (0.165 ml, 0.95 mmol) and cyclohexanecarboxaldehyde (0.161 mL, 1.33 mmol), aldol-functionalised resin was prepared (not shown). LiOOH cleavage, according to General Procedure 9, employing the aldol-functionalised resin preswollen in THF (4 mL), H_2O_2 (0.18 mL, 1.90 mmol) and LiOH (39.9 mg, 0.95 mmol) dissolved in 0.5 mL H_2O, afforded **(2*S*,3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropanoic acid 290** as a colourless oil (23.3 mg, 0.126 mmol, 66%). $[\alpha]_D^{21}$ -8 ° (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.13 (3H, d, *J* 7.0 Hz, C*H*$_3$), 1.36-1.76 (10H, br. m, (C*H*$_2$)$_5$), 2.75 (1H, dq, *J* 7.0, 3.0 Hz, C*H*CH$_3$), 3.67 (1H, dd, *J* 8.5, 3.0 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.9 (CH_3), 26.2 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 40.4 (CH), 41.5 (CH), 76.1 (CH), 182.3 (C). Spectroscopic data identical to literature compound.[128]

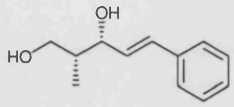
(2*S*,3*R*)-3-hydroxy-2-methyldecanoic acid, 291



According to General Procedure 16, employing *N*-propionyl-oxazolidin-2-one resin **73a** (200 mg, 0.95 mmol/g, 0.19 mmol), 9-BBNOTf (1.90 mL, 0.5 M, 0.95 mmol), $^{i}Pr_2NEt$ (0.165 ml, 0.95 mmol) and octylaldehyde (0.207 mL, 1.33 mmol), aldol-functionalised resin was prepared (not shown). LiOOH cleavage, according to General Procedure 9, employing the aldol-functionalised resin preswollen in THF (4 mL), H_2O_2 (0.18 mL, 1.90 mmol) and LiOH (39.9 mg, 0.95 mmol) dissolved in 0.5 mL H_2O, afforded **(2*S*,3*R*)-3-hydroxy-2-methyldecanoic acid 291** as a colourless oil (19.2 mg, 0.095 mmol, 50%). $[\alpha]_D^{21}$ + 15° (*c* 0.96, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.86 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.15 (3H, d, *J* 7.0 Hz, $CHCH_3$), 1.17-1.52 (12H, m, $(CH_2)_6CH_3$), 2.51 (1H, dd, *J* 7.0, 3.0 Hz, C*H*CH$_3$), 3.89 (1H, m, C*H*OH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 10.7 (CH_3),

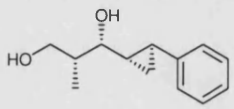
14.5 (CH_3), 23.0 (CH_2), 26.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 32.2 (CH_2), 34.0 (CH_2), 44.4 (CH), 72.1 (CH), 180.9 (C); IR (thin film) ν_{max} (cm^{-1}): 3400 (broad O-H), 1709 (C=O); HRMS (ES^+) for $C_{11}H_{26}NO_3$ $[M+NH_4]^+$ Calc. 220.1913, Found 220.1915.

(*E*,2*R*,3*R*)-2-methyl-5-phenylpent-4-ene-1,3-diol, 293



According to General Procedure 16, employing *N*-propionyl-oxazolidin-2-one resin **73a** (500 mg, 0.90 mmol/g, 0.45 mmol), 9-BBNOTf (4.5 mL, 0.5 M, 2.25 mmol), $^iPr_2NEt$ (0.391 ml, 2.25 mmol) and *trans*-cinnamaldehyde (0.397 mL, 3.15 mmol), aldol-functionalised resin **292** was prepared (not shown). $NaBH_4$ cleavage, according to General Procedure 11, employing functionalised resin **292** (200 mg, 0.90 mmol/g, 0.18 mmol) preswollen in 4ml THF and $NaBH_4$ (34.0 mg, 0.90 mmol) dissolved in 0.5 mL water, afforded **(*E*,2*R*,3*R*)-2-methyl-5-phenylpent-4-ene-1,3-diol 293** (22.5 mg, 0.117 mmol, 65%) as a colourless oil. $[\alpha]_D^{25}$ 11 ° (*c* 0.18, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300MHz): δ 0.96 (3H, d, *J* 7.0 Hz, C*H*$_3$), 2.06 (1H, m, C*H*CH$_3$), 2.15 (2H, s, 2 x O*H*), 3.74 (2H, m, C*H*$_2$OH), 4.50 (1H, m, C*H*OH), 6.30 (1H, dd, *J* 16.0, 6.2 Hz, *H*C=CH), 6.64 (1H, d, *J* 16.0 Hz, HC=C*H*), 7.23 – 7.43 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.8 (CH_3), 40.6 (CH), 66.8 (CH_2), 78.8 (CH), 126.8 (CH), 128.0 (CH), 129.0 (CH), 130.0 (CH), 131.5 (CH), 142.7 (C); HRMS (ES^+) for $C_{12}H_{16}O_2$ $[M+NH_4]^+$ Calc. 210.1489, Found 210.1489. Spectroscopic data identical to literature compound.[129]

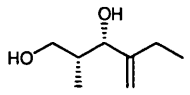
(1*R*,2*R*)-2-methyl-1-((1*S*,2*S*)-2-phenylcyclopropyl)-propane-1,3-diol, 294



Aldol functionalised resin **292** (200mg, 0.9mmol/g, 0.18 mmol) loose in a foil-wrapped flask, was preswollen in DCM (6 mL) and cooled to -10 °C. Diethyl zinc (0.90 ml, 1.0 M, 0.90 mmol) was added, followed immediately by diiodomethane (0.725 mL, 0.90 mmol). The reaction was agitated on an orbital shaker for 2 hours, with the temperature allowed to

warm slowly to 0 °C. After this time, the resin was washed thoroughly with DCM and DCM / MeOH and then dried thoroughly in a vacuum oven at 40 °C. $NaBH_4$ cleavage, according to General Procedure 11, employing functionalised resin (200 mg, 0.90 mmol/g, 0.18 mmol) preswollen in 4ml THF and $NaBH_4$ (34.0 mg, 0.90 mmol) dissolved in 0.5 mL water, afforded **(1*R*,2*R*)-2-methyl-1-((1*S*,2*S*)-2-phenylcyclopropyl)propane-1,3-diol 294** (27.1 mg, 0.131 mmol, 73%) as a white solid. m.p. 91 – 92 °C; $[\alpha]_D^{25}$ 48 ° (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300MHz): δ 0.92 (3H, d, *J* 7.0 Hz, C*H*$_3$), 0.95 (2H, m, *cyc*-C*H*$_2$), 1.27 (1H, m, *cyc*-C*H*), 1.74 (1H, m, *cyc*-C*H*), 1.97 (1H, m, C*H*CH$_3$), 2.65 (2H, s, 2 x O*H*), 3.26 (1H, dd, *J* 8.0, 3.5 Hz, C*H*OH), 3.60 (1H, dd, *J* 10.5, 4.5 Hz, C*H*$_A$H$_B$OH), 3.69 (1H, dd, *J* 10.5, 7.0 Hz, CH$_A$*H*$_B$OH), 6.96-7.21 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 11.9 (CH_3), 13.9 (CH_2), 21.4 (CH), 26.7 (CH), 40.3 (CH), 67.0 (CH_2), 78.8 (CH), 126.1 (CH), 126.2 (CH), 128.8 (CH), 142.6 (C); IR (KBr disc) ν_{max} (cm^{-1}): 3330 (broad O-H); MS (CI+, NH_3) *m/z* (%) 206 (100) $[M+H]^+$, 188 (36) $[M-H_2O]^+$; HRMS (ES^+) for $C_{13}H_{18}O_2$ $[M+NH_4]^+$ Calc. 224.1645, Found 224.1647.

(2*R*,3*S*)-2-methyl-4-methylenehexane-1,3-diol, 296



According to General Procedure 16, employing *N*-propionyl-oxazolidin-2-one resin **73a** (500 mg, 0.90 mmol/g, 0.45 mmol), 9-BBNOTf (4.5 mL, 0.5 M, 2.25 mmol), ^{i}Pr$_2$NEt (0.391 ml, 2.25 mmol) and 2-ethylacrolein (0.308 mL, 3.15 mmol), aldol-functionalised resin **295** was prepared (not shown). $NaBH_4$ cleavage, according to General Procedure 11, employing functionalised resin **295** (200 mg, 0.90 mmol/g, 0.18 mmol) preswollen in 4ml THF and $NaBH_4$ (34.0 mg, 0.90 mmol) dissolved in 0.5 mL water, afforded **(2*R*,3*S*)-2-methyl-4-methylenehexane-1,3-diol 296** (16.1 mg, 0.112 mmol, 62%) as a colourless oil. $[\alpha]_D^{25}$ -26 ° (*c* 0.8, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300MHz): δ 0.84 (3H, d, *J* 7.0 Hz, CHC*H*$_3$), 1.05 (3H, t, *J* 7.0 Hz, CH$_2$C*H*$_3$), 1.80-2.08 (3H, br. m, C*H*CH$_3$, C*H*$_2$CH$_3$), 2.64 (2H, br. s, 2 x O*H*), 3.68 (2H, m, C*H*$_A$H$_B$OH), 4.28 (1H, d, *J* 3.0 Hz, C*H*OH), 4.92 (1H, br. s, C=C*H*$_A$H$_B$), 5.05 (1H, br. s, C=CH$_A$*H*$_B$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.9 (CH_3), 12.6 (CH_3), 25.6 (CH_2), 37.7 (CH), 67.0 (CH_2), 76.4 (CH), 108.5 (CH_2), 152.4 (C); IR (thin

film) ν_{max} (cm^{-1}): 3380 (broad O-H); MS (CI+, NH_3) *m/z* (%) 162 (100) $[M+NH_4]^+$, 144 (23) $[M+H]^+$, 52 (23); HRMS (ES+) for $C_8H_{16}O_2$ $[M+NH_4]^+$ Calc. 162.1489, Found 162.1491.

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Appendix

X-ray crystal structure of (S)-4-(4-Benzyloxy-benzyl)-oxazolidin-2-one 103

The structure and stereochemistry of **103** were proven *via* X-ray crystallography, see Fig.i The asymmetric unit of crystal **103** contains two crystallographically independent molecules, which display similar geometry differing only at the benzyloxy moiety.

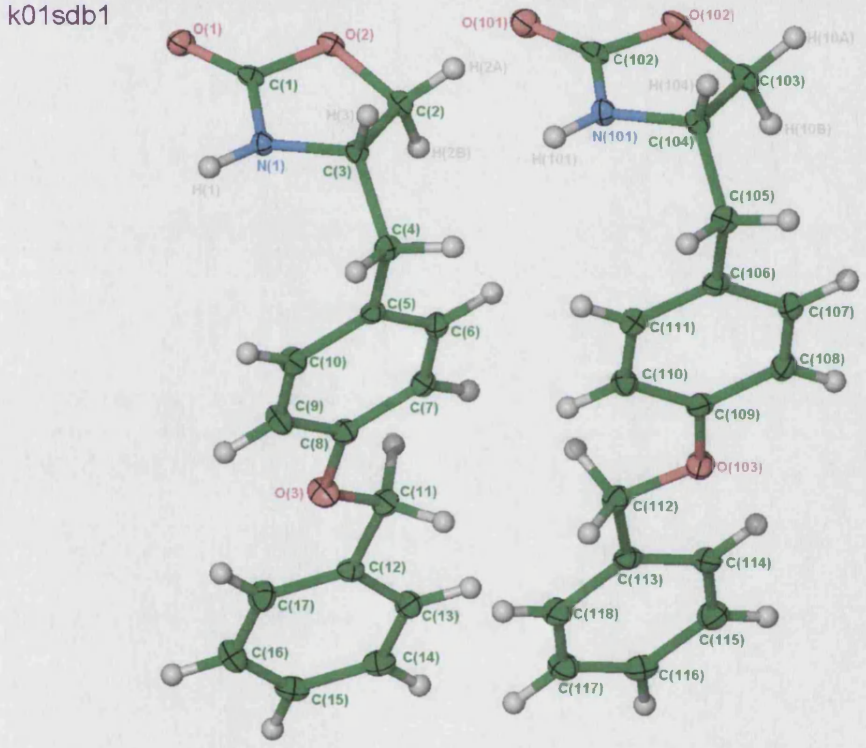

Fig i: *X-ray crystal structure of both conformers of 4-(4-Benzyloxy-benzyl)-oxazolidin-2-one* **103**

***Packing Motif of 4-(4-Benzyloxy-benzyl)-oxazolidin-2-one*, 103**

Fig ii clearly shows the complementary hydrogen-bonding between the carbonyl oxygen and the carbamate hydrogen.

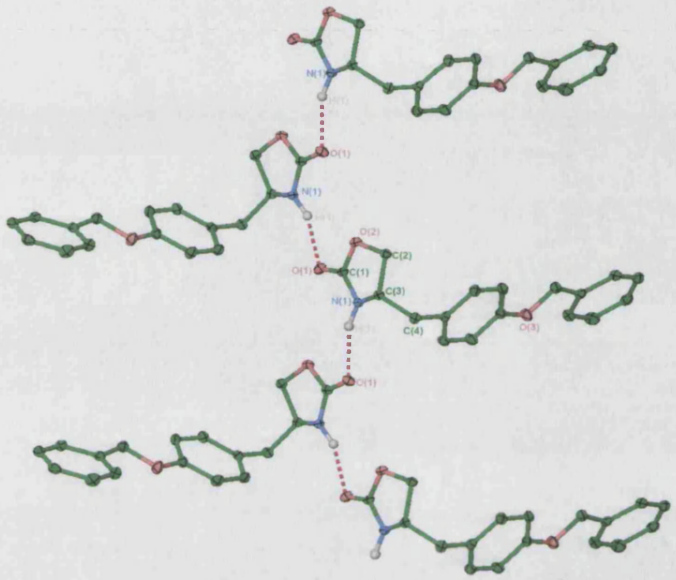

***Fig* ii:** *Packing Motif of 4-(4-Benzyloxy-benzyl)-oxazolidin-2-one* **103**

Table i. *Crystal data and structure refinement for 4-(4-Benzyloxy-benzyl)-oxazolidin-2-one* **103**

Identification code	k01sdb1
Empirical formula	C17 H17 N O3
Formula weight	283.32
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 11.8790(2)Å α = 90o
	b = 8.3820(1)Å β = 103.183(1)o
	c = 14.7910(3)Å γ = 90o
Volume	1433.92(4) Å3
Z	4
Density (calculated)	1.312 Mg/m3
Absorption coefficient	0.090 mm-1
F(000)	600
Crystal size	0.15 x 0.15 x 0.08 mm
Theta range for data collection	2.97 to 27.44o
Index ranges	-15<=h<=15; -10<=k<=10; -19<=l<=19
Reflections collected	28819
Independent reflections	6512 [R(int) = 0.0731]
Reflections observed (>2□)	5417
Data Completeness	0.996
Max. and min. transmission	0.9933 and 0.9866
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	6512 / 3 / 386
Goodness-of-fit on F2	1.066
Final R indices [I>2□(I)]	R1 = 0.0390 wR2 = 0.0932
R indices (all data)	R1 = 0.0560 wR2 = 0.1069
Absolute structure parameter	1.1(7)
Largest diff. peak and hole	0.299 and -0.347 eÅ-3

Note: Chirality of compound cannot be assigned with confidence from the X–ray data.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A	
N1-H1	0.979	1.994	154.35	2.907	O1	[-x, y+1/2, -z+1]
N101-H101	0.912	2.005	158.04	2.871	O101	[-x+1, y+1/2, -z+1]

Table ii. *Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2 x 103) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.*

Atom	x	y	z	U(eq)
O(1)	-428(1)	1036(1)	4886(1)	35(1)
O(2)	1342(1)	103(1)	5525(1)	31(1)
O(3)	1186(1)	3954(2)	9768(1)	43(1)
O(101)	4576(1)	861(2)	4992(1)	42(1)
O(102)	6383(1)	16(1)	5588(1)	37(1)
O(103)	6626(1)	3625(2)	9833(1)	43(1)
N(1)	1109(1)	2721(2)	5461(1)	26(1)
N(101)	6116(1)	2598(2)	5368(1)	31(1)
C(1)	581(1)	1316(2)	5258(1)	26(1)
C(2)	2421(1)	777(2)	6048(1)	30(1)
C(3)	2368(1)	2527(2)	5755(1)	26(1)
C(4)	2960(1)	3706(2)	6502(1)	31(1)
C(5)	2507(1)	3732(2)	7381(1)	29(1)
C(6)	2966(1)	2760(2)	8130(1)	34(1)
C(7)	2550(1)	2774(2)	8941(1)	35(1)
C(8)	1661(1)	3805(2)	9003(1)	31(1)
C(9)	1187(2)	4786(2)	8260(1)	38(1)
C(10)	1602(2)	4749(2)	7457(1)	36(1)
C(11)	1588(2)	2902(2)	10519(1)	36(1)
C(12)	965(1)	3241(2)	11281(1)	31(1)
C(13)	1406(2)	2607(2)	12151(1)	37(1)
C(14)	831(2)	2799(2)	12856(1)	40(1)
C(15)	-178(2)	3639(2)	12708(1)	41(1)
C(16)	-635(2)	4300(3)	11849(1)	48(1)
C(17)	-62(2)	4093(2)	11127(1)	42(1)
C(102)	5601(1)	1183(2)	5288(1)	31(1)
C(103)	7492(1)	746(2)	5978(1)	33(1)
C(104)	7374(1)	2473(2)	5643(1)	29(1)
C(105)	7934(1)	3699(2)	6370(1)	33(1)
C(106)	7551(1)	3656(2)	7278(1)	31(1)
C(107)	8219(1)	2900(2)	8059(1)	38(1)
C(108)	7887(1)	2899(2)	8899(1)	39(1)
C(109)	6872(1)	3662(2)	8969(1)	34(1)
C(110)	6183(2)	4398(2)	8200(1)	35(1)
C(111)	6530(1)	4389(2)	7360(1)	34(1)
C(112)	5556(2)	4261(2)	9910(1)	38(1)
C(113)	5396(1)	4026(2)	10887(1)	34(1)
C(114)	6099(2)	3023(2)	11515(1)	40(1)
C(115)	5898(2)	2829(2)	12404(1)	46(1)
C(116)	5000(2)	3636(2)	12662(1)	43(1)
C(117)	4317(2)	4651(2)	12032(1)	44(1)
C(118)	4514(2)	4841(2)	11154(1)	41(1)

Table iii. *Bond lengths [Å] and angles [o] for 1.*

O(1)-C(1)	1.2221(18)	O(2)-C(1)	1.3579(19)
O(2)-C(2)	1.4518(19)	O(3)-C(8)	1.3805(19)
O(3)-C(11)	1.414(2)	O(101)-C(102)	1.2259(19)
O(102)-C(102)	1.353(2)	O(102)-C(103)	1.448(2)
O(103)-C(109)	1.3752(19)	O(103)-C(112)	1.406(2)
N(1)-C(1)	1.336(2)	N(1)-C(3)	1.4679(19)
N(101)-C(102)	1.328(2)	N(101)-C(104)	1.460(2)
C(2)-C(3)	1.527(2)	C(3)-C(4)	1.529(2)
C(4)-C(5)	1.517(2)	C(5)-C(6)	1.383(2)
C(5)-C(10)	1.396(2)	C(6)-C(7)	1.397(2)
C(7)-C(8)	1.384(2)	C(8)-C(9)	1.384(2)
C(9)-C(10)	1.387(2)	C(11)-C(12)	1.510(2)
C(12)-C(13)	1.381(2)	C(12)-C(17)	1.386(2)
C(13)-C(14)	1.380(2)	C(14)-C(15)	1.364(3)
C(15)-C(16)	1.379(3)	C(16)-C(17)	1.401(3)
C(103)-C(104)	1.526(2)	C(104)-C(105)	1.526(2)
C(105)-C(106)	1.512(2)	C(106)-C(111)	1.389(2)
C(106)-C(107)	1.396(2)	C(107)-C(108)	1.386(2)
C(108)-C(109)	1.389(2)	C(109)-C(110)	1.386(2)
C(110)-C(111)	1.395(2)	C(112)-C(113)	1.513(2)
C(113)-C(118)	1.382(2)	C(113)-C(114)	1.384(2)
C(114)-C(115)	1.398(2)	C(115)-C(116)	1.388(3)
C(116)-C(117)	1.380(3)	C(117)-C(118)	1.380(3)
C(1)-O(2)-C(2)	108.14(11)	C(8)-O(3)-C(11)	117.35(13)
C(102)-O(102)-C(103)	108.64(12)	C(109)-O(103)-C(112)	117.01(13)
C(1)-N(1)-C(3)	111.29(12)	C(102)-N(101)-C(104)	112.50(13)
O(1)-C(1)-N(1)	129.20(15)	O(1)-C(1)-O(2)	120.45(14)
N(1)-C(1)-O(2)	110.35(13)	O(2)-C(2)-C(3)	104.39(12)
N(1)-C(3)-C(2)	99.41(12)	N(1)-C(3)-C(4)	114.30(13)
C(2)-C(3)-C(4)	115.67(13)	C(5)-C(4)-C(3)	115.78(13)
C(6)-C(5)-C(10)	117.75(15)	C(6)-C(5)-C(4)	121.76(15)
C(10)-C(5)-C(4)	120.49(14)	C(5)-C(6)-C(7)	122.05(16)
C(8)-C(7)-C(6)	119.13(15)	O(3)-C(8)-C(7)	124.90(14)
O(3)-C(8)-C(9)	115.35(14)	C(7)-C(8)-C(9)	119.76(15)
C(8)-C(9)-C(10)	120.46(16)	C(9)-C(10)-C(5)	120.84(15)
O(3)-C(11)-C(12)	109.48(14)	C(13)-C(12)-C(17)	118.91(16)
C(13)-C(12)-C(11)	118.46(15)	C(17)-C(12)-C(11)	122.54(14)
C(14)-C(13)-C(12)	120.76(17)	C(15)-C(14)-C(13)	120.46(16)
C(14)-C(15)-C(16)	120.13(17)	C(15)-C(16)-C(17)	119.66(18)
C(12)-C(17)-C(16)	120.06(16)	O(101)-C(102)-N(101)	128.92(16)
O(101)-C(102)-O(102)	120.69(15)	N(101)-C(102)-O(102)	110.38(14)
O(102)-C(103)-C(104)	105.32(12)	N(101)-C(104)-C(105)	113.69(13)
N(101)-C(104)-C(103)	99.82(13)	C(105)-C(104)-C(103)	114.64(13)
C(106)-C(105)-C(104)	116.00(13)	C(111)-C(106)-C(107)	118.09(15)
C(111)-C(106)-C(105)	120.85(15)	C(107)-C(106)-C(105)	121.05(15)
C(108)-C(107)-C(106)	121.21(16)	C(107)-C(108)-C(109)	119.70(15)
O(103)-C(109)-C(110)	124.20(15)	O(103)-C(109)-C(108)	115.57(14)
C(110)-C(109)-C(108)	120.24(15)	C(109)-C(110)-C(111)	119.32(16)
C(106)-C(111)-C(110)	121.43(15)	O(103)-C(112)-C(113)	109.90(14)

C(118)-C(113)-C(114)	119.30(16)	C(118)-C(113)-C(112)	118.53(15)
C(114)-C(113)-C(112)	122.16(15)	C(113)-C(114)-C(115)	119.72(16)
C(116)-C(115)-C(114)	120.56(17)	C(117)-C(116)-C(115)	119.02(17)
C(118)-C(117)-C(116)	120.43(18)	C(117)-C(118)-C(113)	120.96(18)

Table iv. *Anisotropic displacement parameters (Å2 x 103) for 1. The anisotropic displacement factor exponent takes the form: -2 gpi2 [h2 a*2 U11 + ... + 2 h k a* b* U*

Atom	U11	U22	U33	U23	U13	U12
O(1)	30(1)	34(1)	42(1)	-7(1)	10(1)	-7(1)
O(2)	35(1)	23(1)	36(1)	-2(1)	14(1)	0(1)
O(3)	56(1)	48(1)	29(1)	8(1)	16(1)	10(1)
O(101)	34(1)	37(1)	58(1)	-10(1)	15(1)	-8(1)
O(102)	41(1)	23(1)	53(1)	-1(1)	21(1)	1(1)
O(103)	37(1)	63(1)	31(1)	-4(1)	10(1)	7(1)
N(1)	26(1)	23(1)	29(1)	1(1)	6(1)	0(1)
N(101)	29(1)	24(1)	40(1)	2(1)	7(1)	-1(1)
C(1)	32(1)	24(1)	28(1)	-2(1)	16(1)	-1(1)
C(2)	31(1)	29(1)	32(1)	2(1)	10(1)	2(1)
C(3)	25(1)	28(1)	27(1)	0(1)	9(1)	0(1)
C(4)	28(1)	35(1)	32(1)	-2(1)	10(1)	-7(1)
C(5)	26(1)	31(1)	28(1)	-6(1)	6(1)	-6(1)
C(6)	28(1)	42(1)	31(1)	-3(1)	5(1)	5(1)
C(7)	36(1)	39(1)	27(1)	2(1)	2(1)	4(1)
C(8)	34(1)	35(1)	26(1)	0(1)	9(1)	-1(1)
C(9)	43(1)	39(1)	37(1)	6(1)	15(1)	13(1)
C(10)	42(1)	35(1)	31(1)	6(1)	10(1)	3(1)
C(11)	39(1)	38(1)	32(1)	2(1)	8(1)	1(1)
C(12)	34(1)	28(1)	33(1)	-4(1)	10(1)	-6(1)
C(13)	39(1)	33(1)	38(1)	2(1)	6(1)	2(1)
C(14)	52(1)	37(1)	32(1)	-1(1)	10(1)	-6(1)
C(15)	53(1)	37(1)	39(1)	-7(1)	21(1)	-7(1)
C(16)	42(1)	48(1)	57(1)	1(1)	19(1)	11(1)
C(17)	43(1)	44(1)	37(1)	6(1)	5(1)	4(1)
C(102)	36(1)	26(1)	36(1)	-4(1)	18(1)	-1(1)
C(103)	36(1)	29(1)	38(1)	3(1)	16(1)	3(1)
C(104)	29(1)	31(1)	31(1)	2(1)	13(1)	2(1)
C(105)	30(1)	33(1)	38(1)	1(1)	13(1)	-6(1)
C(106)	30(1)	32(1)	34(1)	-5(1)	10(1)	-7(1)
C(107)	29(1)	46(1)	38(1)	-4(1)	8(1)	4(1)
C(108)	33(1)	51(1)	31(1)	-2(1)	3(1)	4(1)
C(109)	33(1)	39(1)	30(1)	-6(1)	8(1)	-5(1)
C(110)	31(1)	37(1)	38(1)	-2(1)	11(1)	0(1)
C(111)	34(1)	35(1)	34(1)	1(1)	8(1)	-1(1)
C(112)	33(1)	44(1)	37(1)	-5(1)	8(1)	-3(1)
C(113)	34(1)	34(1)	35(1)	-9(1)	9(1)	-8(1)
C(114)	40(1)	41(1)	39(1)	-9(1)	10(1)	2(1)
C(115)	53(1)	43(1)	40(1)	-1(1)	4(1)	2(1)

C(116)	52(1)	45(1)	33(1)	-9(1)	13(1)	-9(1)
C(117)	41(1)	51(1)	44(1)	-10(1)	17(1)	0(1)
C(118)	39(1)	44(1)	40(1)	-5(1)	11(1)	0(1)

Table v. *Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2 x 103) for 1.*

Atom	x	y	z	U(eq)
H(2A)	3092	236	5890	36
H(2B)	2480	678	6724	36
H(3)	2711	2640	5200	32
H(4A)	3795	3452	6673	38
H(4B)	2880	4791	6231	38
H(6)	3582	2061	8092	41
H(7)	2874	2086	9443	42
H(9)	574	5490	8302	46
H(10)	1266	5424	6951	43
H(11A)	2431	3046	10758	43
H(11B)	1447	1785	10307	43
H(13)	2114	2033	12266	44
H(14)	1140	2343	13448	48
H(15)	-567	3770	13197	49
H(16)	-1334	4893	11747	57
H(17)	-378	4536	10532	50
H(10A)	8116	197	5756	40
H(10B)	7669	699	6665	40
H(104)	7705	2583	5082	35
H(10C)	8782	3541	6507	40
H(10D)	7772	4776	6097	40
H(107)	8914	2378	8014	45
H(108)	8351	2378	9424	47
H(110)	5482	4904	8244	42
H(111)	6058	4895	6833	41
H(11C)	4922	3723	9462	45
H(11D)	5527	5413	9759	45
H(114)	6716	2468	11343	48
H(115)	6381	2140	12835	56
H(116)	4857	3491	13263	51
H(117)	3707	5222	12204	53
H(118)	4037	5543	10728	49
H(1)	670	3685	5235	44(5)
H(101)	5714(14)	3513(19)	5183(12)	44(6)

***X-ray crystal structure for Lactone* 274**

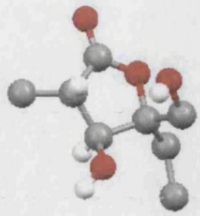

Table vi. *Crystal data and structure refinement for* **274**

Identification code	c:\x-ray\kappa\k05rg1\maxus\k05rg1
Empirical formula	C8 H14 O4
Formula weight	174.19
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 5.4370(2)Å α = 90°
	b = 14.1610(6)Å β = 101.723(2)°
	c = 5.9280(2)Å γ = 90°
Volume	446.90(3) $Å^3$
Z	2
Density (calculated)	1.294 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	188
Crystal size	0.18 x 0.18 x 0.03 mm
Theta range for data collection	5.46 to 27.47°
Index ranges	-6<=h<=7; -18<=k<=18; -7<=l<=7
Reflections collected	8674
Independent reflections	2025 [R(int) = 0.0559]
Reflections observed (>2σ)	1779
Data Completeness	0.989
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2025 / 1 / 116
Goodness-of-fit on F^2	1.149
Final R indices [I>2σ(I)]	R^1 = 0.0554 wR_2 = 0.0926
R indices (all data)	R^1 = 0.0679 wR_2 = 0.0959
Absolute structure parameter	0.3(13)
Largest diff. peak and hole	0.191 and -0.154 $eÅ^{-3}$

Notes: absolute configuration assigned on basis of known stereochemistry at one chiral centre. Lattice dominated by hydrogen bonded sheets in *ac* plane.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O3-H3	0.840	1.897	169.72	2.728	O4 [x, y, z+1]
O4-H4A	0.840	1.924	167.70	2.750	O2 [x-1, y, z]
O4-H4A	0.840	2.621	134.98	3.269	O1 [x-1, y, z]

Table vii. *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.*

Atom	x	y	z	U(eq)
O(1)	8345(3)	8800(1)	9406(2)	31(1)
O(2)	9941(3)	7395(1)	8907(3)	37(1)
O(3)	3756(3)	8476(2)	12861(2)	41(1)
O(4)	3461(3)	8491(1)	7400(2)	39(1)
C(1)	6453(4)	9224(2)	10561(4)	32(1)
C(2)	8566(4)	7873(2)	9808(3)	31(1)
C(3)	6985(4)	7555(2)	11478(4)	33(1)
C(4)	6210(4)	8485(2)	12435(3)	31(1)
C(5)	8376(5)	6859(2)	13253(4)	45(1)
C(6)	4074(4)	9335(2)	8710(4)	35(1)
C(7)	7494(5)	10172(2)	11493(4)	40(1)
C(8)	5845(5)	10676(2)	12916(5)	47(1)

Table viii. *Bond lengths [Å] and angles [°] for 1.*

O(1)-C(2)	1.335(3)	O(1)-C(1)	1.474(2)
O(2)-C(2)	1.210(3)	O(3)-C(4)	1.407(2)
O(4)-C(6)	1.427(3)	C(1)-C(7)	1.517(3)
C(1)-C(6)	1.525(3)	C(1)-C(4)	1.550(3)
C(2)-C(3)	1.506(3)	C(3)-C(5)	1.526(3)
C(3)-C(4)	1.527(3)	C(7)-C(8)	1.527(3)
C(2)-O(1)-C(1)	111.29(17)	O(1)-C(1)-C(7)	106.57(17)
O(1)-C(1)-C(6)	106.11(16)	C(7)-C(1)-C(6)	111.7(2)
O(1)-C(1)-C(4)	103.15(18)	C(7)-C(1)-C(4)	114.57(19)
C(6)-C(1)-C(4)	113.71(19)	O(2)-C(2)-O(1)	120.8(2)
O(2)-C(2)-C(3)	127.5(2)	O(1)-C(2)-C(3)	111.6(2)
C(2)-C(3)-C(5)	112.2(2)	C(2)-C(3)-C(4)	102.95(18)
C(5)-C(3)-C(4)	115.90(18)	O(3)-C(4)-C(3)	113.69(19)
O(3)-C(4)-C(1)	110.93(18)	C(3)-C(4)-C(1)	104.21(16)
O(4)-C(6)-C(1)	112.0(2)	C(1)-C(7)-C(8)	113.45(19)

Table ix. *Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement factor exponent takes the form:* $-2\,\pi^2 [\, h^2 a^{*2} U11 + ... + 2\, h\, k\, a^*\, b^*\, U$

Atom	U11	U22	U33	U23	U13	U12
O(1)	28(1)	40(1)	28(1)	0(1)	12(1)	-5(1)
O(2)	38(1)	44(1)	31(1)	-7(1)	11(1)	-3(1)
O(3)	34(1)	71(1)	19(1)	-2(1)	9(1)	-13(1)
O(4)	33(1)	65(1)	20(1)	-2(1)	9(1)	-9(1)
C(1)	31(1)	43(1)	24(1)	0(1)	12(1)	-1(1)
C(2)	28(1)	41(2)	22(1)	-4(1)	3(1)	-8(1)
C(3)	33(1)	42(2)	22(1)	-2(1)	5(1)	-12(1)
C(4)	31(1)	44(1)	19(1)	-2(1)	5(1)	-7(1)
C(5)	59(2)	43(2)	31(1)	5(1)	5(1)	-5(1)
C(6)	34(1)	47(2)	26(1)	5(1)	13(1)	-3(1)
C(7)	38(1)	44(2)	42(1)	-3(1)	14(1)	-8(1)
C(8)	57(2)	49(2)	39(1)	-6(1)	17(1)	-6(1)

Table x. *Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.*

Atom	x	y	z	U(eq)
H(3)	3822	8436	14286	60(8)
H(4A)	2238	8224	7801	41(7)
H(3A)	5445	7238	10591	39
H(4)	7423	8644	13891	38
H(5A)	9903	7157	14124	67
H(5B)	8828	6297	12464	67
H(5C)	7289	6676	14311	67
H(6A)	2658	9506	9449	41
H(6B)	4312	9856	7662	41
H(7A)	7681	10581	10186	48
H(7B)	9185	10075	12464	48
H(8A)	5700	10286	14248	71
H(8B)	4172	10782	11963	71
H(8C)	6606	11285	13450	71